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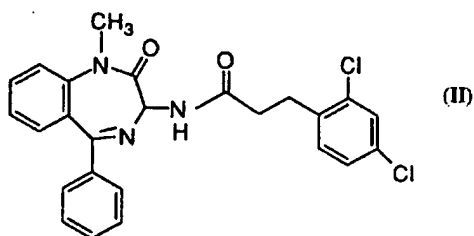
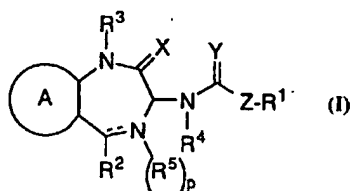


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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/55, C07D 243/24		A1	(11) International Publication Number: WO 95/14471
			(43) International Publication Date: 1 June 1995 (01.06.95)
(21) International Application Number: PCT/US94/13414		(74) Common Representative: MERCK & CO., INC. ; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).	
(22) International Filing Date: 21 November 1994 (21.11.94)		(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).	
(30) Priority Data: 156,331 22 November 1993 (22.11.93) US			
(60) Parent Application or Grant (63) Related by Continuation US 156,331 (CON) Filed on 22 November 1993 (22.11.93)			
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(54) Title: ANTIARRHYTHMIC BENZODIAZEPINES



(57) Abstract

Benzo-(1,5)-diazepine derivatives with an amide or urea function in the 3-position are useful in the treatment of arrhythmia. The compounds have structural formulae (I) and (II).

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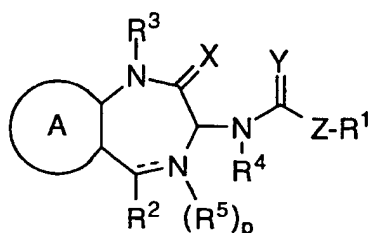
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TITLE OF THE INVENTION

ANTIARRHYTHMIC BENZODIAZEPINES

SUMMARY OF THE INVENTION

5 This invention is concerned with a novel method of treating arrhythmia by the administration of a compound of general structural formula:



I

15 The invention is also concerned with pharmaceutical formulations comprising one or more of the novel compounds as active ingredient, either alone or in combination with one or more of a Class I, Class II or Class IV antiarrhythmic agent.

BACKGROUND OF THE INVENTION

25 Arrhythmias often occur as complications to cardiac diseases such as myocardial infarction and heart failure. In a serious case, arrhythmias give rise to a ventricular fibrillation and can cause sudden death.

30 Though various antiarrhythmic agents are now available on the market, those, having both satisfactory effects and high safety, have not been obtained. For example, antiarrhythmic agents of Class I according to the classification of Vaughan-Williams which cause a selective inhibition of the maximum velocity of the upstroke of the action potential (Vmax) are inadequate for preventing ventricular fibrillation. In addition, they have problems regarding safety, namely, they cause a depression of the myocardial contractility and have a

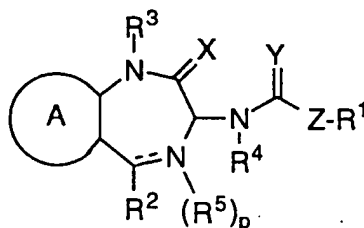
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tendency to induce arrhythmias due to an inhibition of the impulse conduction. Beta-adrenoceptor blockers and calcium antagonists which belong to Class II and IV respectively, have a defect that their effects are either limited to a certain type of arrhythmia or are contraindicated because of their cardiac depressant properties in certain patients with cardiovascular disease. Their safety, however, is higher than that of the antiarrhythmic agents of Class I.

Antiarrhythmic agents of Class III are drugs which cause a selective prolongation of the duration of the action potential without a significant depression of the V_{max} . Drugs in this class are limited. Examples such as Sotalol and amiodarone have been shown to possess Class III properties. Sotalol also possesses Class II effects which may cause cardiac depression and be contraindicated in certain susceptible patients. Also, amiodarone is severely limited by side effects. Drugs of this class are expected to be effective in preventing ventricular fibrillations. Pure Class III agents, by definition, are not considered to cause myocardial depression or an induction of arrhythmias due to the inhibition of the action potential conduction as seen with Class I antiarrhythmic agents.

DETAILED DESCRIPTION OF THE INVENTION

The compounds useful in the novel method of treatment of this invention have structural formula:



or a pharmaceutically acceptable salt thereof, wherein

- 3 -

A is

- 1) thieno,
- 2) pyrido, or
- 3) benzo either unsubstituted or substituted with -NH₂
-NHSO₂ (C₁₋₃ alkyl), C₁₋₃ alkyl or C₁₋₃ alkoxy;

X is

- 1) =O,
- 2) =S,
- 3) =N-NH₂,
- 4) =N-OH or
- 5) =H₂;

Y is

- 1) =O,
- 2) =N-CN or
- 3) =H₂;

Z is

- 1) C₁₋₆ alkylene, either straight or branch chain and either unsubstituted or substituted with phenyl or spiro-piperidine,
- 2) C₂₋₄ alkenylene, either straight or branch chain,
- 3) -(CH₂)_m-W-(CH₂)_n- wherein m and n are independently 0, 1, 2, 3 or 4 and W is -O-, -S- or -NH,
- 4) 4-(5-methylisoxazole-3-yl),
- 5) C₃₋₆ cycloalkylene, or
- 6) single bond;

p is 0 or 1;

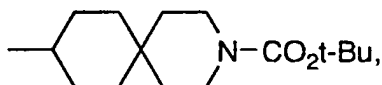
R¹ is

- 1) phenyl, either unsubstituted or substituted with one or two substituents selected from

- 4 -

- 5
- a) -NO₂,
 - b) -Cl, Br, F, or I,
 - c) -CF₃,
 - d) -C₁₋₃ alkyl,
 - e) -C₁₋₃ alkoxy,
 - f) -CN,
 - g) -methylenedioxy,
 - 2) C₅₋₇ cycloalkyl,
 - 3)

10



- 15
- 4) mono- or bicyclic heterocyclyl of 5 to 10 members one or two of which are sulfur, nitrogen or oxygen, the remaining being carbon, such as 2-thienyl, 2-furanyl, 2-indolyl, 2-quinoxolinyl, or 2-(2,3-dihydro benzofuranyl)
 - 5) C₁₋₃ alkyl, or
 - 6) indan-5-yl;

20 R² is

- 1) phenyl, either unsubstituted or substituted with C₁₋₃ alkoxy or 4,4-dimethyloxazolin-2-yl,
 - 2) C₁₋₆ alkyl, either straight or branched chain, and either unsubstituted or substituted with C₁₋₃ alkoxy or C₁₋₃ alkoxy-C₁₋₃ alkoxy,
 - 25 3) C₅₋₇ cycloalkyl,
 - 4) 2- or 3-furyl,
 - 5) 1-methylpiperidin-2-yl, or
 - 6) if R² is phenyl, the 2-position of the phenyl can be joined to the 4-position nitrogen of the diazepine ring through a carbonyl group and the double bond between the 4-nitrogen and the 5-carbon becomes a single bond;
- 30

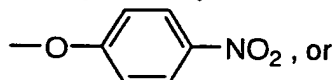
- 5 -

R³ is

- 1) hydrogen or
- 2) C₁-3 alkyl either unsubstituted or substituted with
-N(CH₃)₂, -OH, -CF₃, or
- 5 3) -CF₃;

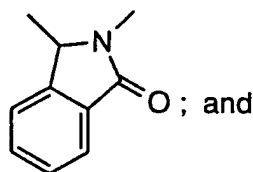
R⁴ is

- 1) hydrogen,
- 2) C₁-6 alkyl, the chain of carbon atoms of which can be
10 interrupted by one or two non-adjacent oxygen atoms and
which is either unsubstituted or substituted with C₁-3
alkoxycarbonyl, -OH or



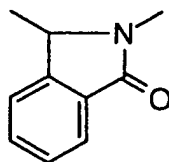
- 15 3) tetrazol-5-yl;

R⁵ is hydrogen or oxygen or is joined to R² to form the partial
structure:



25 the bond represented by ----- is:

- 1) a double bond when p is zero or when p is 1 and R⁵ is
oxygen, or
- 2) a single bond when R⁵ is hydrogen or R⁵ is joined to R² to
form the partial structure:



- 6 -

This invention is meant to include the individual diastereomers where such exist and mixtures thereof and enantiomers and mixtures of the enantiomers.

The pharmaceutically acceptable salts of the compounds of Formulas I include the conventional non-toxic salts or the quaternary ammonium salts of the compounds of Formula I formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

One embodiment of this invention are novel compounds useful in the novel method of treatment of this invention wherein:

A is benzo;

X and Y are oxygen;

R³ is methyl;

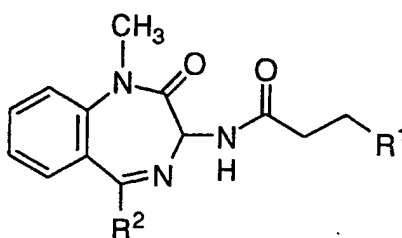
R⁴ is hydrogen; and

R² is C₁₋₆ alkyl.

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Specific novel compounds representative of this embodiment are those of the following structure and specified in Table I:

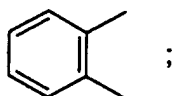
TABLE I



	R ¹	R ²
	2,4-diClPh	-CH ₃
	2,4-diClPh	-C ₂ H ₅
	2,4-diClPh	-t-Bu
	4-CF ₃ Ph	i-C ₃ H ₇
	cyclohexyl	i-C ₃ H ₇
	2,4-diClPh	i-C ₃ H ₇

Another embodiment of the compounds useful in the novel method of treatment of this invention is that wherein:

A is



30

X and Y are oxygen;

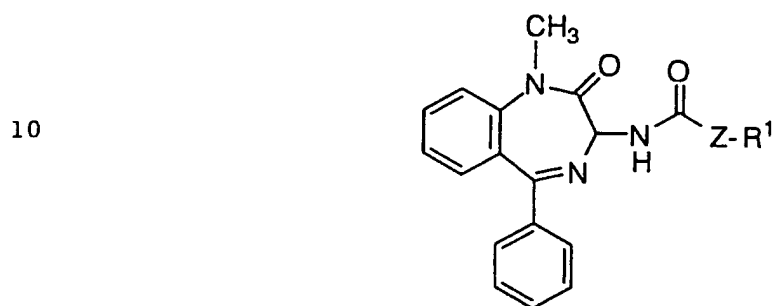
R³ is methyl;

- 8 -

R⁴ is hydrogen; and

R² is phenyl.

A class of novel compounds within this embodiment is that with structural formula:



wherein Z is C₁-6 alkylene or a bond and R¹ is phenyl, phenyl substituted with -Cl, -Br, -I, -F, or -CF₃, or R¹ is cyclohexyl.

Specific novel compounds representative of this class are those depicted in the following Table II:

TABLE II

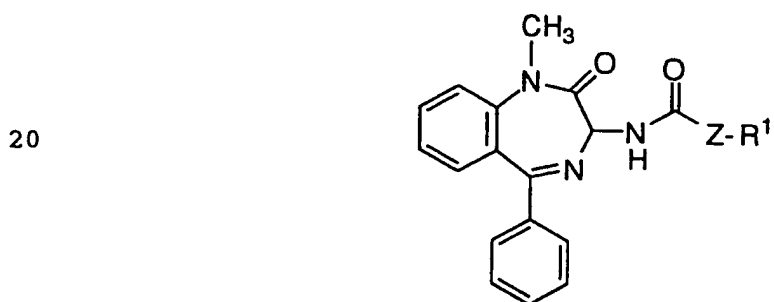
Z	R ¹
-(CH ₂) ₂ -	2,4-diClPh
-(CH ₂) ₂ -	4-ClPh
-(CH ₂) ₂ -	2,4-diFPh
-(CH ₂) ₂ -	2-ClPh
-(CH ₂) ₂ -	4-CF ₃ Ph
-CH ₂ -	4-CF ₃ Ph
-(CH ₂) ₂ -	3-CF ₃ Ph
-(CH ₂) ₂ -	2-CF ₃ Ph
-(CH ₂) ₂ -	cyclohexyl
-	cyclohexyl

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TABLE II (Cont'd)

	Z	R ¹
	-(CH ₂) ₃ -	cyclohexyl
5	-CH ₂ -	cyclohexyl
	-(CH ₂) ₂ -	Ph
	-CH ₂ -	Ph
	-(CH ₂) ₂ -	4-CNPh
	-(CH ₂) ₂ -	3-ClPh
10	-(CH ₂) ₃ -	Ph
	-(CH ₂) ₂ -	3-CNPh
	-(CH ₂) ₃	2-thienyl

Another class of novel compounds within this embodiment
 15 is that with structural formula:



25 wherein Z is C₂-4 alkenylene and R¹ is phenyl or phenyl substituted
 with -Cl, -Br, -F, -I, -CF₃, C₁-3 alkyl, C₁-3 alkoxy or methylenedioxy.

30

- 10 -

Specific novel compounds representative of this class are those depicted in the following Table III:

TABLE III

5	<u>Z</u>	<u>R¹</u>
	-CH=CH-	4-NO ₂ Ph
10	-CH=CH-	2,4-diClPh
	-CH=CH-	3-ClPh
15	-CH=CH-	2-ClPh
	-CH=CH-	2,4-diFPh
20	-CH=CH-	2,6-diClPh
	-CH=CH-	4-CF ₃ Ph
25	-CH=CH-	2-BrPh

30

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TABLE III (Cont'd)

	<u>Z</u>	<u>R¹</u>
5	-CH=CH-	4-IPh
	-CH=CH-	4-BrPh
10	$\begin{array}{c} \text{-C=CH-} \\ \\ \text{CH}_3 \end{array}$	Ph
	-CH=CH-	Ph*
15	-CH=CH-	3,4-diClPh
	-CH=CH-	4-CH ₃ Ph
20	-CH=CH-	4-CH ₃ OPh
	-CH=CH-	3,4-methylenedioxyPh
25	-CH=CH-	3-BrPh

*This compound is known in U.S. Patent 4,820,834

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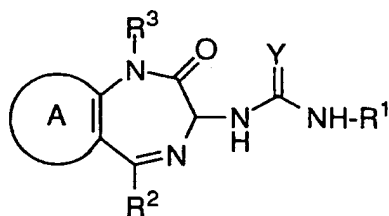
A third embodiment of the compounds useful in the novel method of treatment of this invention is that wherein:

Z is -NH-.

Compounds representative of this embodiment are those disclosed in the following Table IV.

TABLE IV

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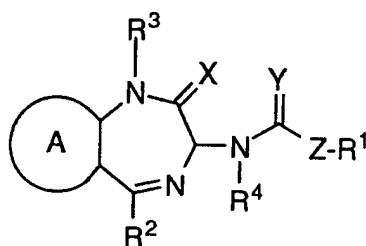
	A	R ¹	R ²	R ³	Y
	benzo	3-CH ₃ Ph	Ph		O
20	benzo	2,4-diClPh	Ph	-CH ₃	O
	benzo	3-CH ₃ Ph		n-C ₃ H ₇	O
25	benzo	-CH ₂ Cyclohexyl	Ph	-CH ₃	=N-CN
	benzo	3-CH ₃ Ph	Ph	-CH ₃	O
30	benzo	5-indanyl	Ph		O
		3-CH ₃ Ph	Ph	-CH ₃	O

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Other specific compounds included within the broadest genus but not included in one of the embodiments previously described are as shown in Table V.

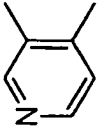
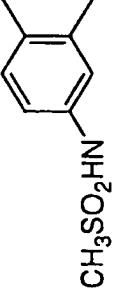
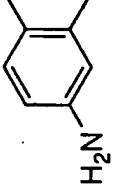
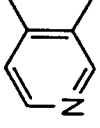
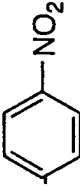
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TABLE V



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TABLE V

A	Z	R ¹	R ²	R ³	R ⁴	X	Y
	-(CH ₂) ₂ -	2,4-diClPh	Ph	CH ₃	H	O	O
	-(CH ₂) ₂ -	2,4-diClPh	Ph	CH ₃	H	O	O
	-(CH ₂) ₂ -	2,4-diClPh	Ph	CH ₃	H	O	O
	-(CH ₂) ₂ -	cyclohexyl	Ph	CH ₃	H	O	O
benzo	-CH ₂ O-	4-NO ₂ Ph	Ph	CH ₃ -(CH ₂) ₂ -O-		O	H ₂

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TABLE V (Cont'd)

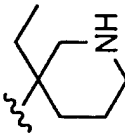
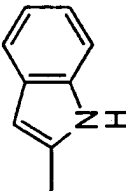

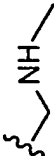
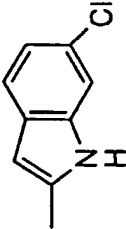

A	Z	R ¹	R ²	R ³	R ⁴	X	Y
benzo	-CH ₂ O-	4-NO ₂ Ph	Ph	CH ₃	H	O	H ₂
benzo	-(CH ₂) ₂ -	2-CH ₃ OPh	Ph	CH ₃	CH ₃	O	H ₂
benzo	-CH=CH-	4-ClPh	Ph	CH ₃	H	O	H ₂
benzo	-(CH ₂) ₂ -	4-ClPh	Ph	CH ₃	H	O	H ₂
benzo		4-ClPh	Ph	CH ₃	H	O	O

TABLE V (Cont'd)

A	Z	R ¹	R ²	R ³	R ⁴	X	Y
benzo	—		Ph	CH ₃	H	O	O
benzo		Ph	Ph	CH ₃	H	O	O
benzo		2-ClPh	Ph	CH ₃	H	O	O
benzo	—		Ph	CH ₃	H	O	O
benzo		Ph	Ph	CH ₃	H	O	O

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TABLE V (Cont'd)




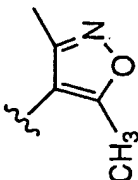
A	Z	R ¹	R ²	R ³	R ⁴	X	Y
benzo	—	Ph	Ph	CH ₃	H	O	O
benzo		Ph	Ph	CH ₃	H	O	O
benzo		Ph	Ph	CH ₃	H	O	O
benzo		2,4-diClPh	Ph	CH ₃	H	O	O
benzo		Ph	Ph	CH ₃	H	O	O

TABLE V (Cont'd)

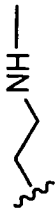
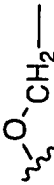
A	Z	R ¹	R ²	R ³	R ⁴	X	Y
benzo		Ph	Ph	CH ₃	H	O	O
benzo		Ph	Ph	CH ₃	H	S	O
benzo	-(CH ₂) ₄ -	-CH ₃	Ph	-CH ₃	$\begin{array}{c} \text{---}(\text{CH}_2)_2\text{O} \\ \\ \text{CH}_3\text{O}(\text{CH}_2)_2 \end{array}$	O	O
benzo	-(CH ₂) ₄ -	-CH ₃	Ph	-CH ₃	-(CH ₂) ₅ OH	O	O
benzo	-(CH ₂) ₃ -	-CH ₃	Ph	CH ₃	H	O	O

TABLE V (Cont'd)

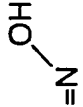
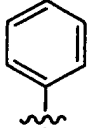
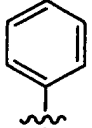
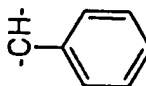
A	Z	R ¹	R ²	R ³	R ⁴	X	Y
benzo	-(CH ₂) ₄ -	-CH ₃	Ph	CH ₃	H	O	O
benzo	-(CH ₂) ₅ -	-CH ₃	Ph	CH ₃	H	O	O
benzo	-(CH ₂) ₂ -	-CH-(CH ₃) ₂	Ph	CH ₃	H	O	O
benzo	-(CH ₂) ₂ -	cyclohexyl	Ph	CH ₃	(tetrazol-1-yl)- methyl	O	O
benzo	-(CH ₂) ₂ -	cyclohexyl	Ph	H	H		O

TABLE V (Cont'd)

A	Z	R ¹	R ²	R ³	R ⁴	X	Y
benzo	-(CH ₂) ₂ -	2,4-diClPh			CH ₃	H O	O O
benzo	-(CH ₂) ₄ S-	-CH ₃	Ph	CH ₃	H O	O O	
benzo	-(CH ₂) ₂ -	cyclohexyl	Ph	CH ₃	H S	O O	
benzo	-(CH ₂) ₂ -	cyclohexyl	Ph	CH ₃	H H ₂	O O	
benzo		Ph	Ph	CH ₃	H O	O O	

- 21 -

TABLE V (Cont'd)

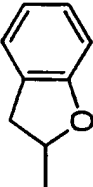
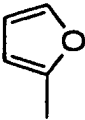
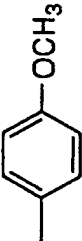
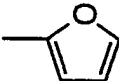
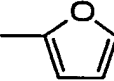
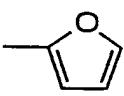
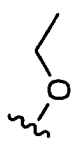
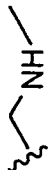
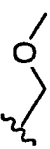
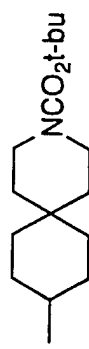
A	Z	R ¹	R ²	R ³	R ⁴	X	Y
benzo	—		Ph	CH ₃	H	O	O
benzo	-(CH ₂) ₂ -		Ph	CH ₃	H	O	O
benzo	-(CH ₂) ₂ -	2,4-diClPh		CH ₃	H	O	O
benzo	-(CH ₂) ₂ -	cyclohexyl		CH ₃	H	O	O
benzo	-(CH ₂) ₂ -	4-CF ₃ Ph		CH ₃	H	O	O

TABLE V (Cont'd)

A	Z	R ¹	R ²	R ³	R ⁴	X	Y
benzo	-(CH ₂) ₂ -	2,4-diClPh		CH ₃	H	O	O
benzo		Ph	cyclohexyl	CH ₃	H	O	O
benzo		Ph	Ph	CH ₃	H	O	O
benzo		2,4-diClPh	Ph	CH ₃	H	O	O
benzo	—		Ph	CH ₃	H	O	O

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TABLE V (Cont'd)

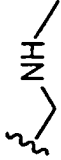
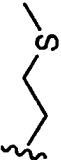
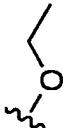



A	Z	R ¹	R ²	R ³	R ⁴	X	Y
benzo		4-CF ₃ Ph	Ph	CH ₃	H	O	O
benzo		Ph	Ph	CH ₃	H	O	O
benzo		Ph	Ph	CH ₃	H	O	O
benzo		2,4-diClPh	Ph		H	O	O
benzo		cyclohexyl	Ph	H	H	S	O

TABLE V (Cont'd)


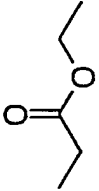

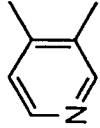
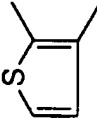
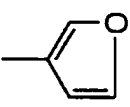
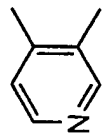
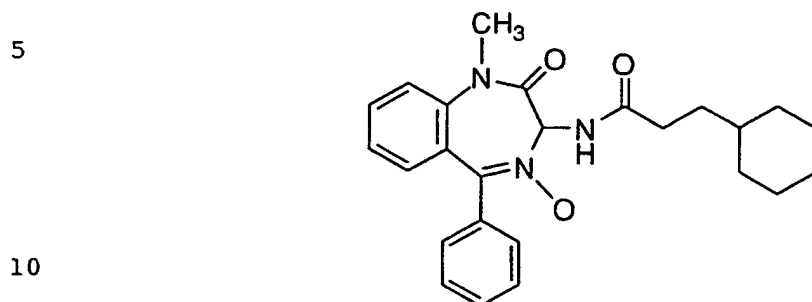
A	Z	R ¹	R ²	R ³	R ⁴	X	Y
benzo		cyclohexyl	Ph	CH ₃		O	O
benzo	-(CH ₂) ₄ -	CH ₃	Ph	CH ₃		O	O
	-(CH ₂) ₂ -	2,4-diClPh	Ph	CH ₃	H	O	O
	-(CH ₂) ₂ -	cyclohexyl	Ph	CH ₃	H	O	O

TABLE V (Cont'd)

A	Z	R ¹	R ²	R ³	R ⁴	X	Y
benzo	-(CH ₂) ₂ -	cyclohexyl	Ph	H	H	=N-NH ₂	O
benzo	-(CH ₂) ₂ -	cyclohexyl	Ph	CH ₃	(tetrazol-2-yl)-methyl	O	O
benzo	-(CH ₂) ₂ -	4-CF ₃ Ph		CH ₃	H	O	O
benzo	-(CH ₂) ₂ -	cyclohexyl	cyclohexyl	CH ₃	H	O	O
	-(CH ₂) ₂ -	4-CF ₃ Ph	Ph	CH ₃	H	O	O
benzo	-(CH ₂) ₂ -	cyclohexyl	3-furyl	CH ₃	H	O	O
benzo	-(CH ₂) ₂ -	cyclohexyl	Ph	CH ₃	CH ₂ CO ₂ Et	O	O
benzo	-(CH ₂) ₄ -	CH ₃	Ph	CH ₃	CH ₂ CO ₂ Et	O	O
benzo	-(CH ₂) ₄ -	CH ₃	Ph	CH ₃	-CH ₂ OH	O	O

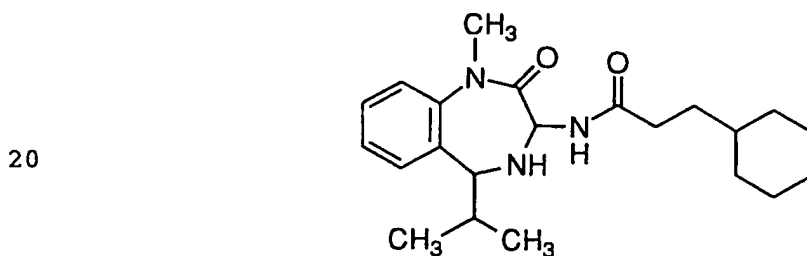
- 26 -

Representative of compounds wherein p is 1 is the compound of structural formula:



Representative of compounds wherein the bond between the 4 and 5 positions is a single bond is the compound of structural formula:

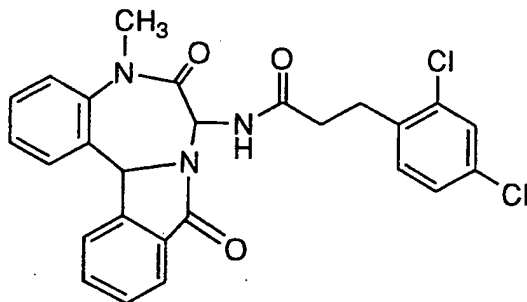
15



Representative of compounds wherein the bond ----- represents a single bond and R⁵ is joined to R² is the compound of structural formula:

30

- 27 -

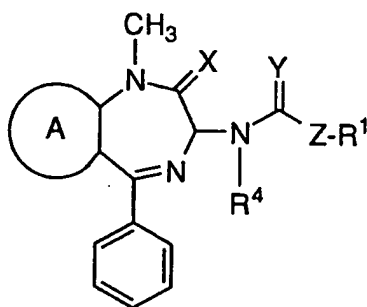


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Another embodiment of this invention is a group of compounds, active in the novel method of treatment of this invention, which are novel compounds per se. These novel compounds are depicted in the following Table VI.

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25

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TABLE VI

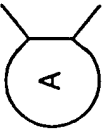
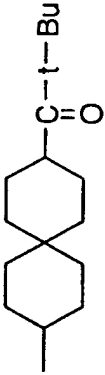
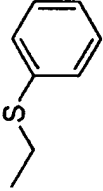
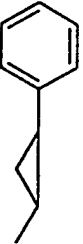
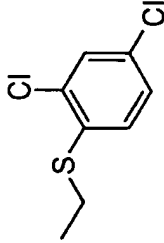
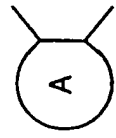
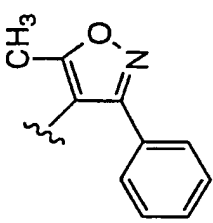

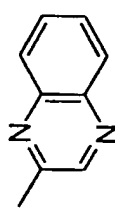
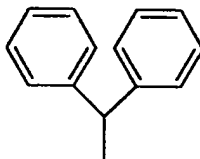


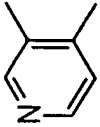
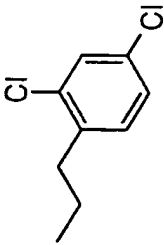
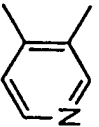
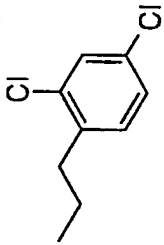
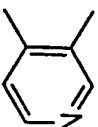
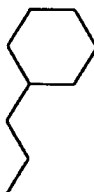
Ex. No.		R ⁴	X	Y	-Z-R ¹
44	benzo	H	O	O	
55	benzo	H	O	O	
3	benzo	H	O	O	
56	benzo	H	O	O	

TABLE VI

Ex. No.		R ⁴	X	Y	-Z-R ¹
38	benzo	H	O	O	
6	benzo	H	O	O	
49	benzo	H	O	O	
22	benzo	H	O	O	

- 30 -

TABLE VI

Ex. No.					-Z-R ¹
		R ⁴	X	Y	
80		H	O	O	
77		H	O	O	
78		H	O	O	

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TABLE VI

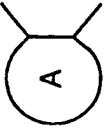
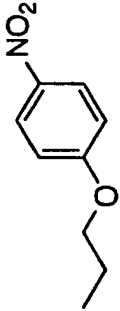
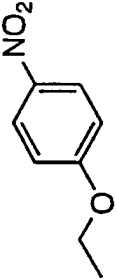
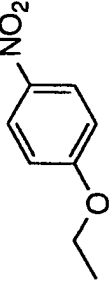
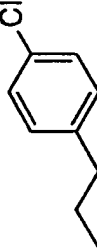
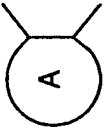
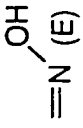
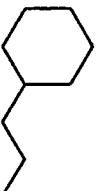
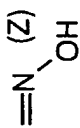
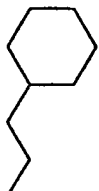
Ex. No.		R ⁴	X	Y	-Z-R ¹
62	benzo		O	H ₂	
63	benzo	H	O	H ₂	
64	benzo	H	O	H ₂	

TABLE VI

Ex. No.		R ⁴	X	Y	-Z-R ¹
70	benzo	H		O	
70	benzo	H		O	

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The compounds useful in the novel method of treatment of the present invention, have the pharmacological properties required for the antiarrhythmic agents of Class III, namely the prolongation of the myocardial action potential in vitro, without a significant depression of the Vmax, and the prolongation of QTc-interval in anesthetized dogs.

These compounds are effective in treating and preventing all types of arrhythmias including ventricular and atrial (supraventricular) arrhythmias. The compounds of the present invention are especially useful to control reentrant arrhythmias and prevent sudden death due to the ventricular fibrillation. These compounds are also effective in treating and preventing impaired cardiac pump functions.

In the novel method of this invention of treating arrhythmia, one of the compounds or pharmaceutically acceptable salt thereof, is administered in an amount ranging from about 0.0001 to about 20 mg per kg or body weight per day, preferably from about 0.001 to about 10 mg per kg of body weight per day in a single dose or in 2 to 4 divided doses.

These compounds can be administered as the sole active ingredient or in combination with other antiarrhythmic agents or other cardiovascular agents.

These compounds, or pharmaceutically acceptable salts thereof, in the described dosages, are administered orally, intraperitoneally, subcutaneously, intramuscularly, transdermally, sublingually or intravenously. They are preferably administered intravenously or orally, for example in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum, or the like prepared by art recognized procedures. The amount of active compound in such therapeutically useful compositions or preparations is such that a suitable dosage will be obtained.

The activity of the compounds described herein as antiarrhythmic agents is measured by their ability to block the IKs and IKr as determined by the following test protocol.

- 34 -

Outward potassium currents are measured in single guinea pig ventricular myocytes using a whole-cell voltage clamp technique described in detail elsewhere (Sanguinetti and Jurkiewicz, 1990. Two components of cardiac delayed activifier K^+ current: differential sensitivity to block by Class III antiarrhythmic agents. J. Gen Physiol. 96: 195-215). Myocytes are isolated by enzymatic (collagenase and protease) digestion of Langendorf perfused hearts. Single cells are then voltage clamped using 1 mm square-bore pipettes filled with 0.5 M Kgluconate, 25 mM KCl, 5 mM K(2)ATP. Cells are bathed in a solution containing, in mM: 132 NaCl, 4KCl, 1.2 MgCl₂, 10 HEPES, 10, glucose: pH 7.2, temp. 35°C.

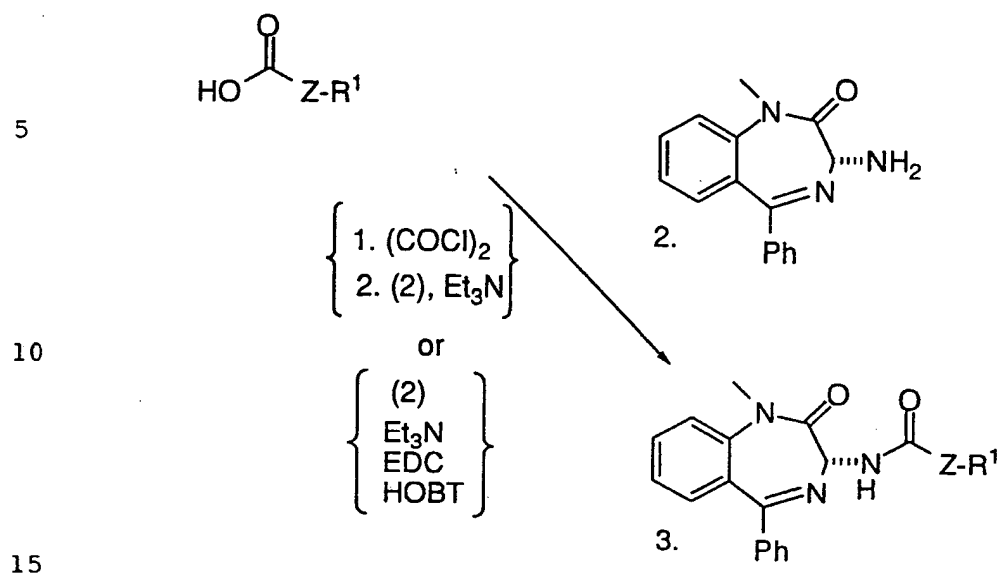
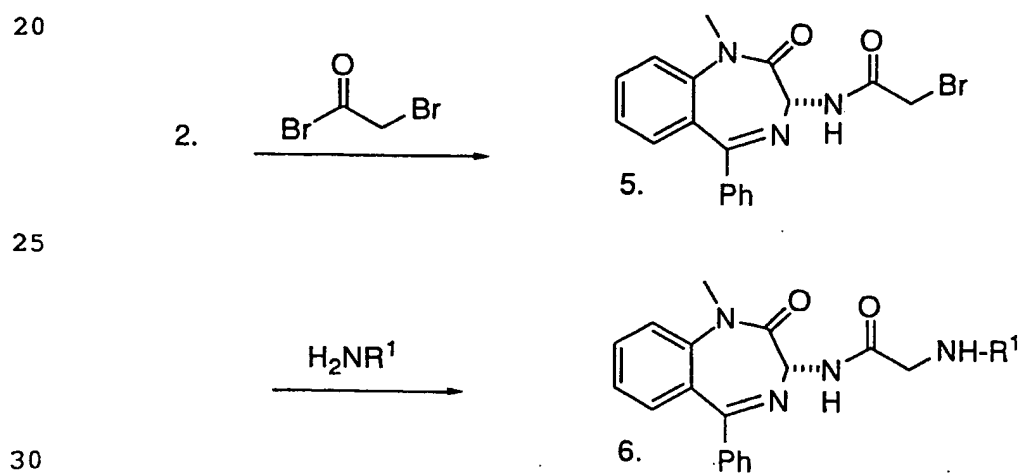
Each cell is maintained at a holding potential of -50 mV. Test depolarizations are applied as voltage ramps from -85 to -50 mV, and as steps to -10 mV (0.5 s) and +50 mV (1.0 s). $I[KI]$ is measured as peak outward current during the voltage ramp. $I[Kr]$ is measured as tail currents upon repolarization from -10 mV to -50 mV. $I[KS]$ is measured as time-dependent current during the pulse to +50 mV. Currents are measured during control, then after exposure to drug at two different concentrations.

Employing this test the compounds described herein have an IC_{50} of less than 1000 nM as IKs and/or IKr blockers.

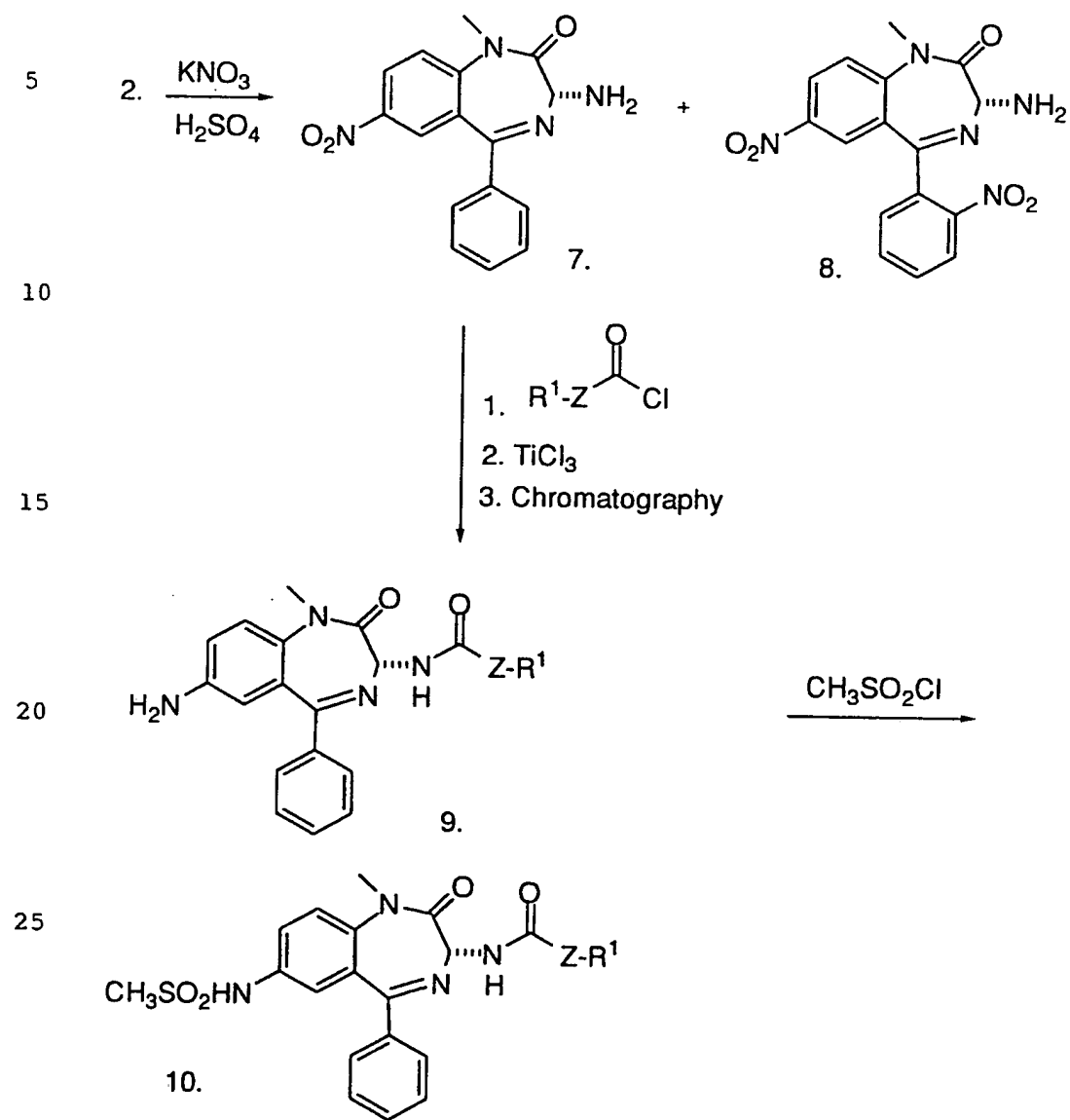
The compounds useful in the novel method of treatment of this invention are either known in the art or are structurally similar to compounds known in the art and known to have CCK-B antagonist activity. See for example U.S. Patents 4,820,834 and 5,004,741 by Evans et al. Processes for the preparation of the named compounds are therefore obvious to one skilled in the art. Typical synthetic schemes employed in making the compounds herein are illustrated below.

30

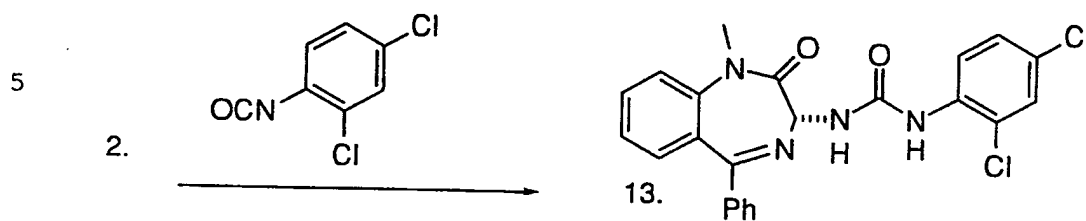
- 35 -

SCHEME 1SCHEME 2

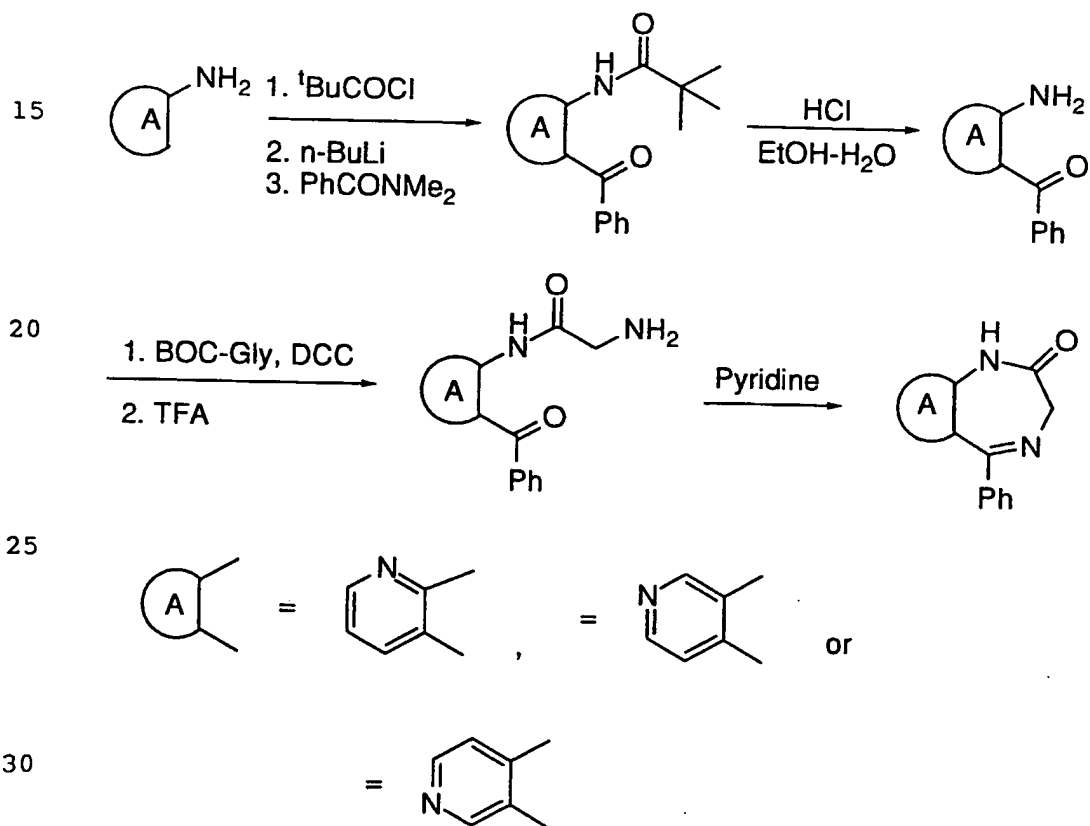
- 36 -

SCHEME 3

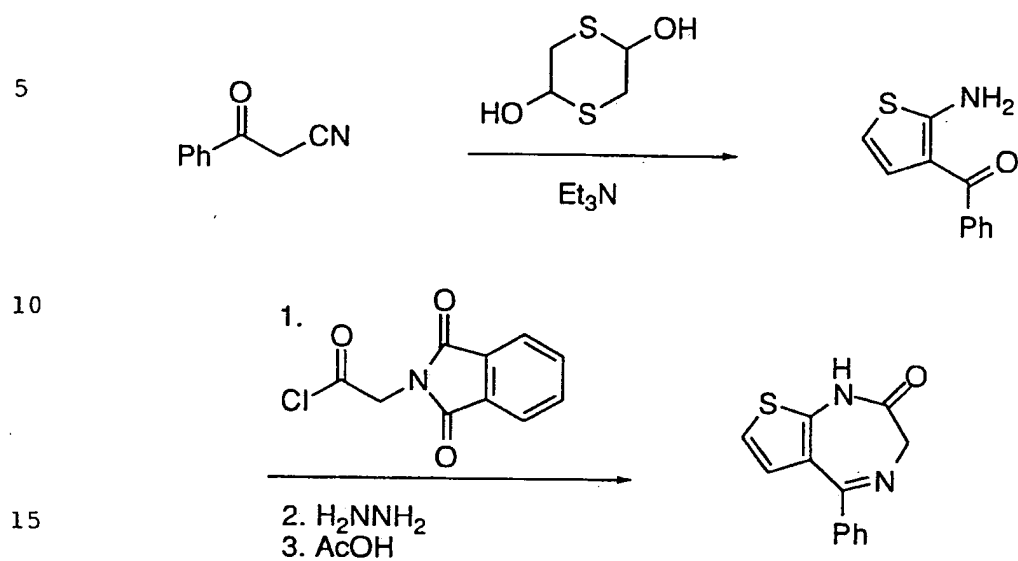
- 37 -

SCHEME 4

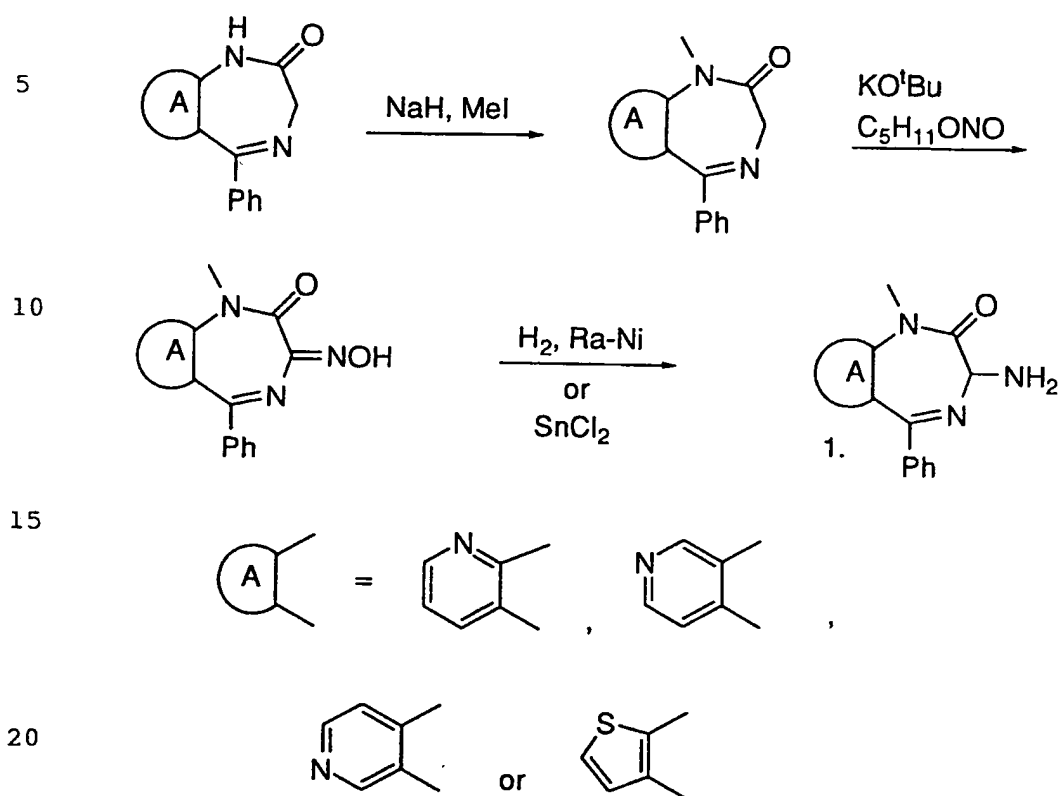
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SCHEME 5

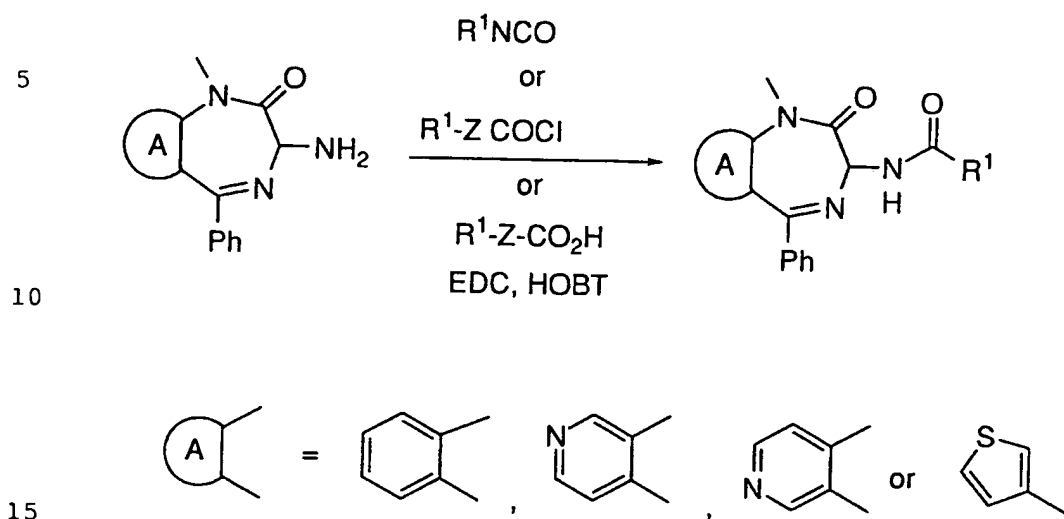
- 38 -

SCHEME 6

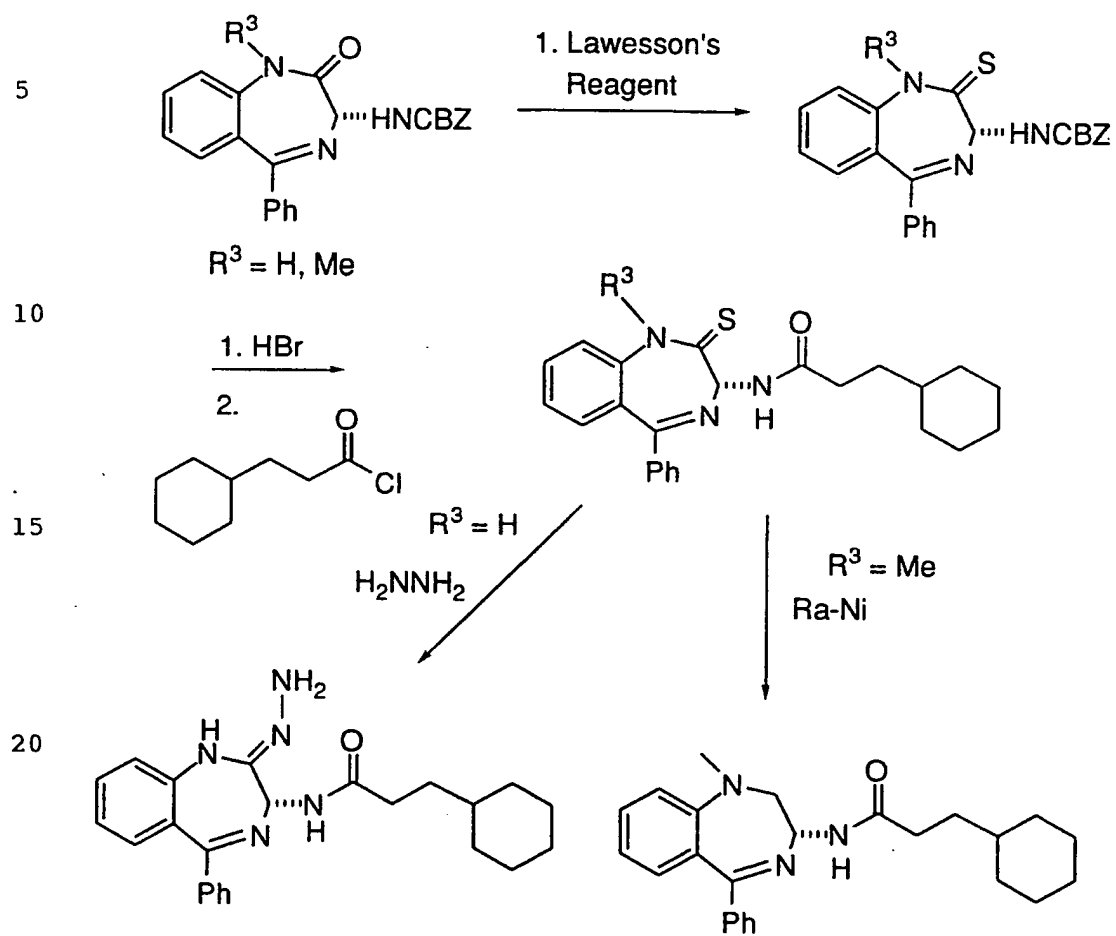
- 39 -

SCHEME 7

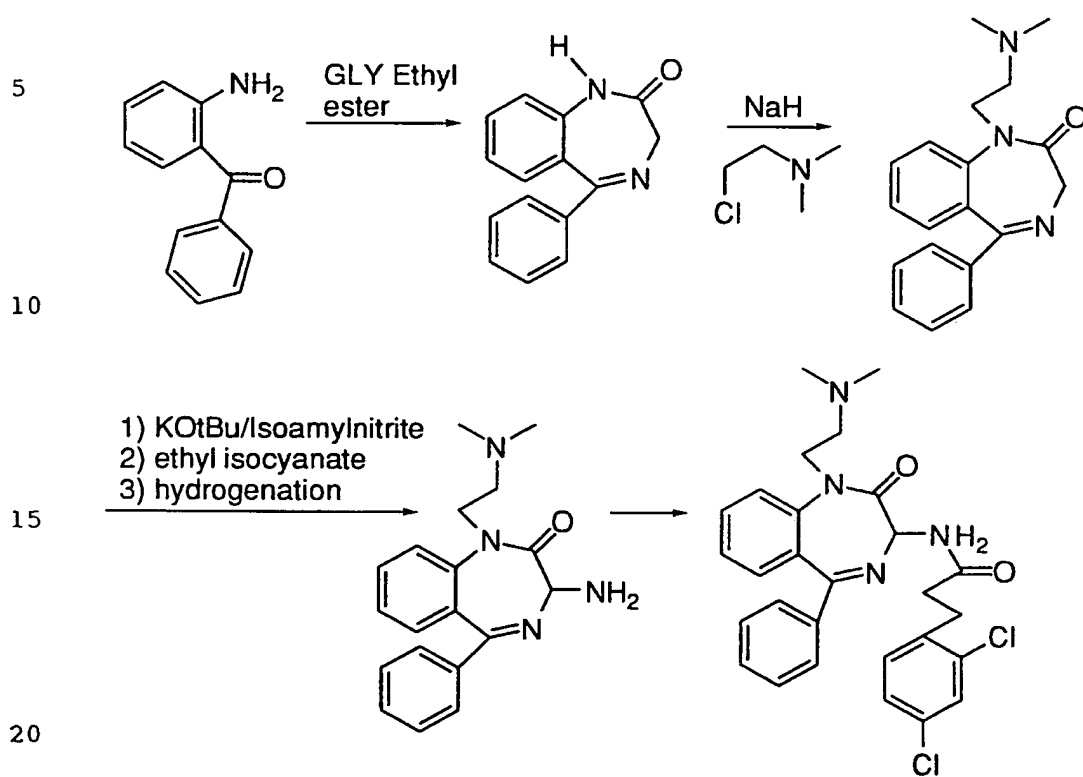
- 40 -

SCHEME 8

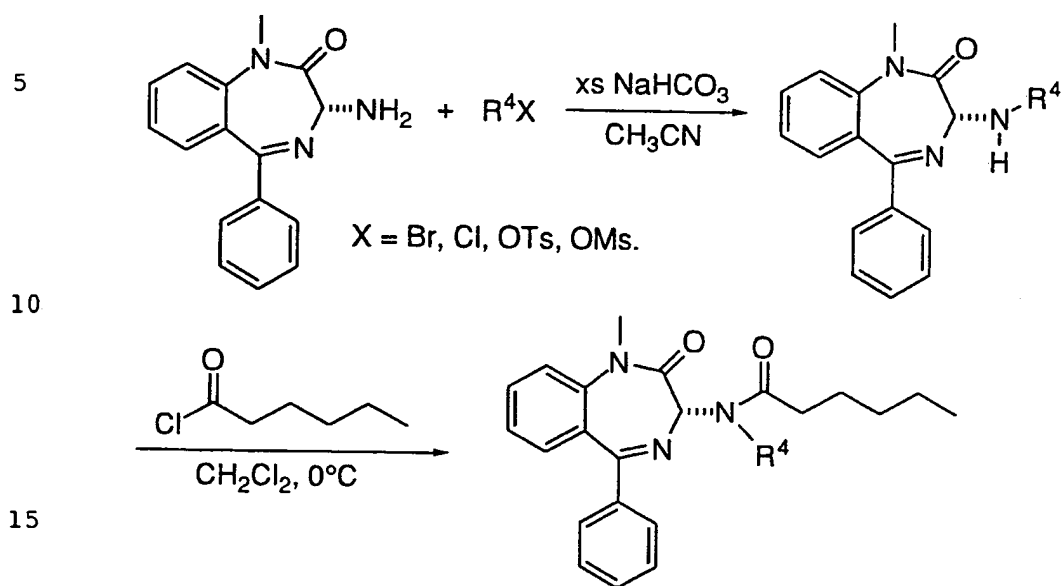
- 41 -

SCHEME 9

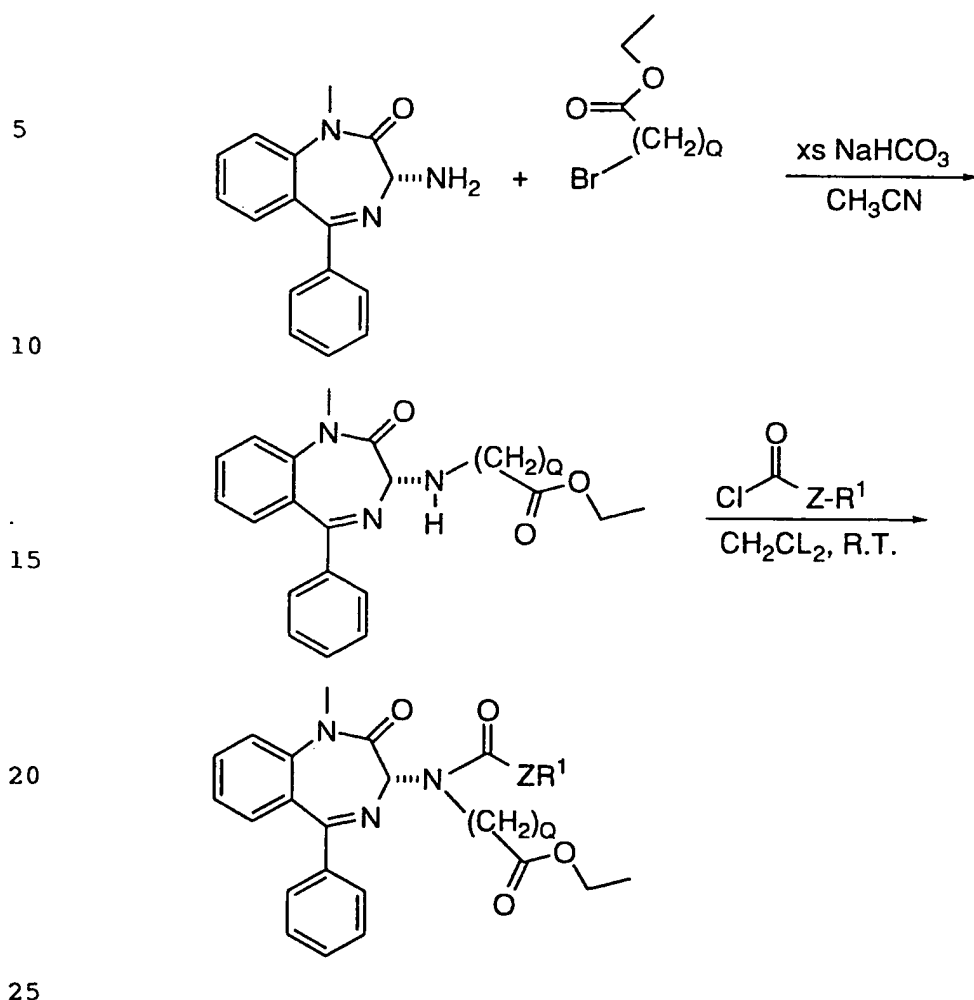
- 42 -

SCHEME 10

- 43 -

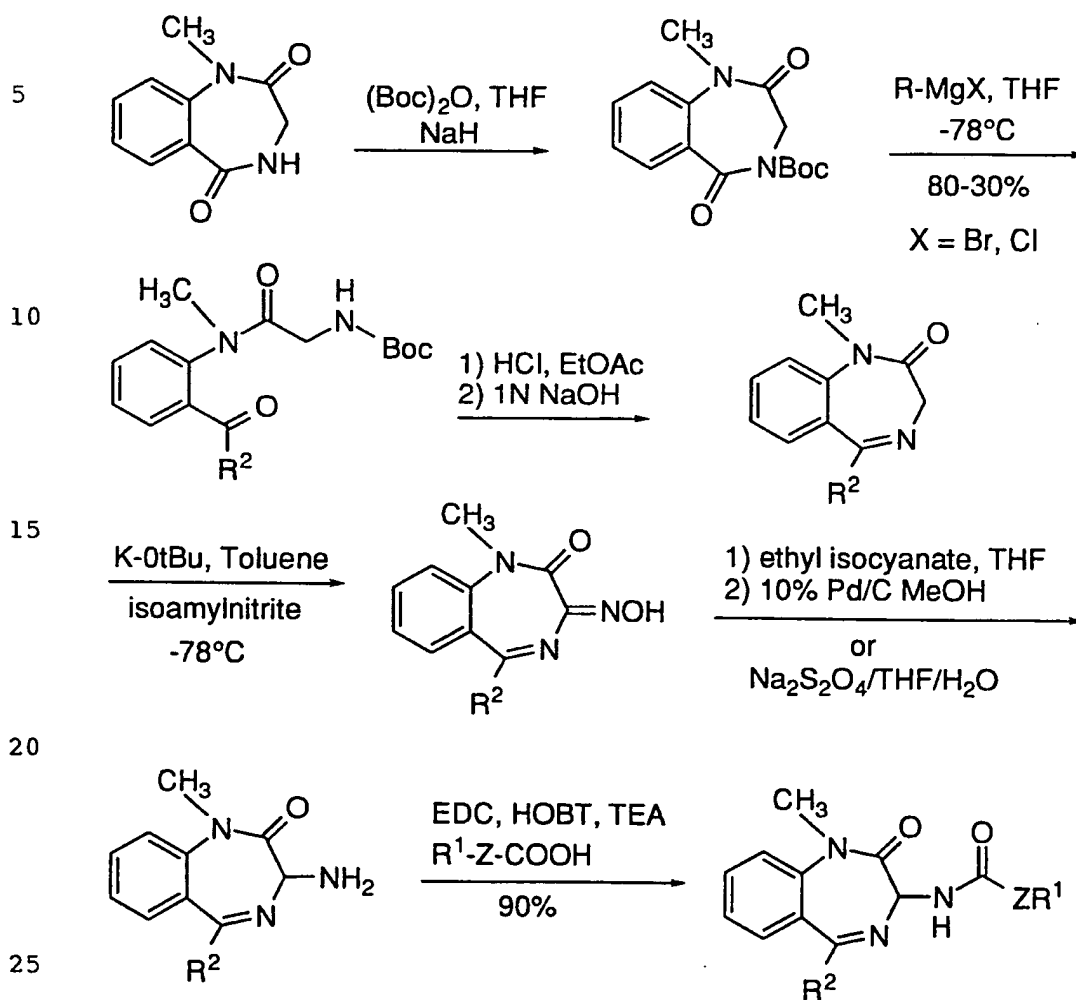
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- 44 -

SCHEME 12

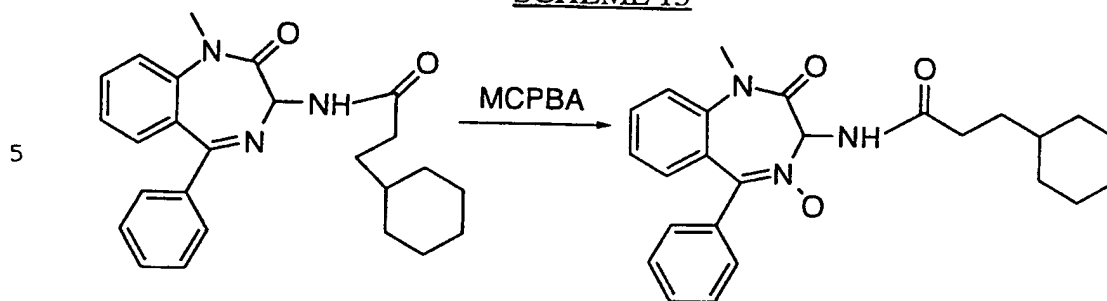
- 45 -

SCHEME 13



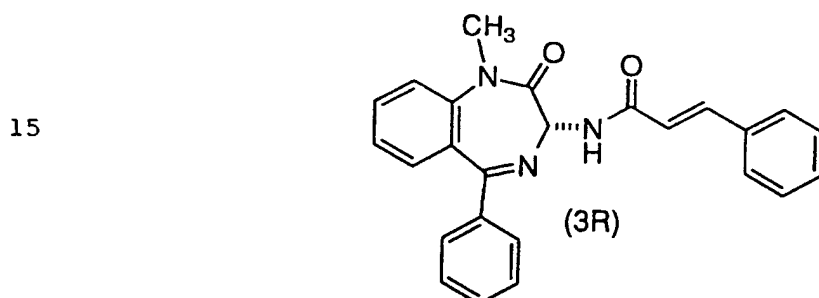
- 47 -

SCHEME 15



10

EXAMPLE 1



20 (E)-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-phenyl-2-propenamide

A solution of (E)-3-phenyl-2-propenoyl chloride (367 mg, 2.2 mmol) in methylene chloride (1 mL) was added to a solution of 3(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (*J. Org. Chem.* 1987, 52, 3232-3239) (531 mg, 2.0 mmol) and triethylamine (307 μ L, 225 mg, 2.2 mmol) in methylene chloride (10 mL). The mixture was stirred at room temperature for 25 min. and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (95:5) and the residue was triturated with Et_2O . The solid was collected and dried *in vacuo* at 70°C to give (E)-(+)-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-phenyl-2-propenamide as a colorless solid (170 mg, 21%), m.p. 140-142°C, $[\alpha]_D^{25} +86.7^\circ$ ($c=0.173$, CH_2Cl_2).

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δ H (CDCl₃) 7.70-7.26 (16H, m), 6.63 (1H, d, J 15.6 Hz), 5.68 (1H, d, J 8.3 Hz), and 3.50 (3H, s).

Anal. Calcd. for C₂₅H₂₁N₃O₂·0.15 (C₂H₅)₂O:

C, 75.63; H, 5.58; N, 10.33.

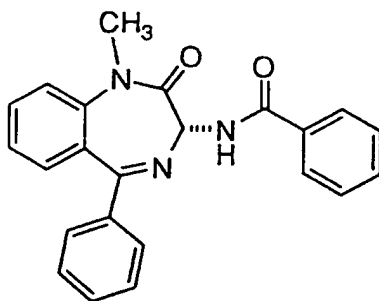
5 Found: C, 75.29; H, 5.57; N, 10.33%.

Employing the procedure substantially as described above, but substituting an appropriate acid chloride for the (E)-3-phenyl-2-propenoyl chloride, the following compounds were prepared:

10

EXAMPLE 2

15



20

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]benzamide

m.p. 224-225°C, [α]_D +89.2° (c = 0.141, CH₂Cl₂).

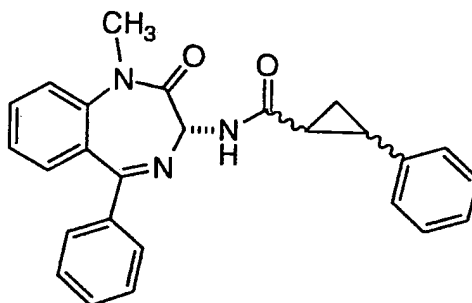
25 δ H (CDCl₃) 8.04 (1H, d, J 8.1 Hz), 7.96 (2H, d, J 6.8 Hz), 7.64-7.36 (10H, m), 7.27 (2H, t, J 7.6 Hz), 5.74 (1H, d, J 7.8 Hz), and 3.51 (3H, s).

Anal. Calcd. for C₂₃H₁₉N₃O₂·0.20H₂O:

C, 74.06; H, 5.24; N, 11.26.

30 Found: C, 74.13; H, 5.12; N, 11.16%.

- 49 -

EXAMPLE 3

10 First diastereoisomer to elute:

(-)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-(trans-2-phenyl-1-cyclopropane)carboxamide

m.p. 180-181°C, $[\alpha]_D -155.8^\circ$ (c = 0.434, CH₂Cl₂).

15 δ_H (CDCl₃) 7.62-7.09 (15H, m), 5.59 (1H, d, J 8.1 Hz), 3.47 (3H, s),
2.52-2.45 (1H, m), 1.90-1.84 (1H, m), 1.69-1.56 (1H, m), and 1.38-1.32
(1H, m).

Anal. Calcd. for C₂₆H₂₃N₃O₂·0.25H₂O:

C, 75.43; H, 5.72; N, 10.15.

20 Found: C, 75.38; H, 5.64; N, 9.94%.

Second diastereoisomer to elute:

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-(trans-2-phenyl-1-cyclopropane)carboxamide

m.p. 104-107°C, $[\alpha]_D +328.2^\circ$ (c = 0.098, CH₂Cl₂).

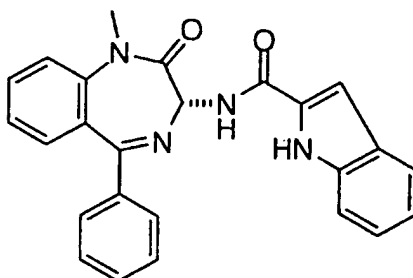
25 δ_H (CDCl₃) 7.62-7.13 (15H, m), 5.60 (1H, d, J 8.3 Hz), 3.48 (3H, s),
2.59-2.54 (1H, m), 1.93-1.87 (1H, m), 1.62-1.56 (1H, m, overlaps with
water), and 1.33-1.25 (1H, m).

Anal. Calcd. for C₂₆H₂₃N₃O₂·0.50H₂O·0.45PhCH₃:

C, 76.13; H, 5.95; N, 9.14.

30 Found: C, 76.10; H, 5.94; N, 9.17%.

- 50 -

EXAMPLE 4

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4--
benzodiazepin-3-yl]-1H-indole-2-carboxamide

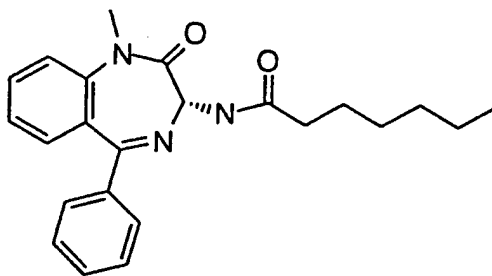
m.p. 167-177°C, $[\alpha]_D +113^\circ$ (c = 1.103, CH₂Cl₂).

δ_H (CDCl₃) 9.15 (1H, br s), 8.10 (1H, d, J 9.0 Hz), 7.75-7.10 (14H, m),
 5.75 (1H, d, J 9.0 Hz), and 3.50 (3H, s).

Anal. Calcd. for C₂₅H₂₀N₄O₂:

C, 73.51; H, 4.94; N, 13.72.

Found: C, 73.31; H, 4.80; N, 13.62%.

EXAMPLE 5

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]heptanamide

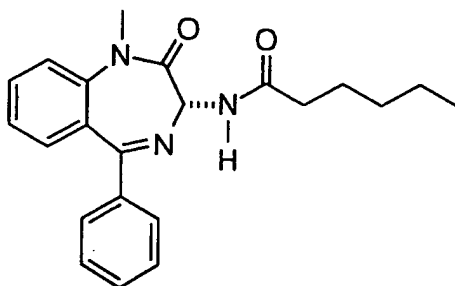
m.p. 49-54°C, $[\alpha]_D +69.5^\circ$ (c=1.000, MeOH).

Anal. Calcd. for C₂₃H₂₇N₃O₂·0.40H₂O:

C, 71.81; H, 7.28; N, 10.92.

Found: C, 71.90; H, 7.09; N, 10.85%.

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EXAMPLE 6

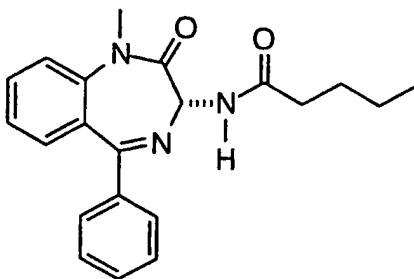
(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]hexanamide

$[\alpha]_D^{+72.6^\circ}$ (c=0.920, MeOH).

Anal. Calcd. for $C_{22}H_{25}N_3O_2$:

C, 72.70; H, 6.93; N, 11.56.

Found: C, 72.44; H, 6.75; N, 11.25%.

EXAMPLE 7

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]pentanamide

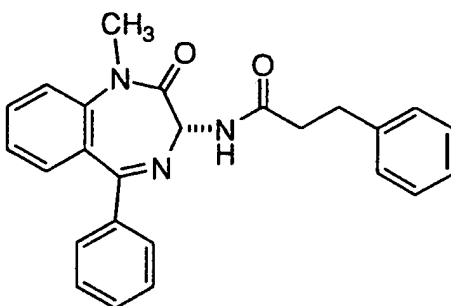
$[\alpha]_D^{+68.2^\circ}$ (c=1.310, MeOH).

Anal. Calcd. for $C_{21}H_{23}N_3O_2 \cdot 0.25CHCl_3$:

C, 68.21; H, 6.26; N, 11.26.

Found: C, 68.2; H, 6.29; N, 11.17%.

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EXAMPLE 8

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-phenylpropanamide

Oxalyl chloride (158 μ L, 230 mg, 1.81 mmol) was added to a mixture of 3-phenylpropanoic acid (249 mg, 1.66 mmol) and DMF (1 drop) in THF (10 mL) and the mixture was stirred at room temperature for 40 min. 3(R)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (*J. Org. Chem.* 1987, 52, 3232-3239) (400 mg, 1.51 mmol) and triethylamine (252 μ L, 183 mg, 1.81 mmol) were added and the mixture was stirred at room temperature for 18 h. The mixture was poured into saturated aqueous sodium hydrogen carbonate (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (95:5) and the residue was recrystallized from toluene/hexane to give (+)-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-phenylpropanamide as a colorless solid (380 mg, 63%), m.p. 179°C, $[\alpha]_D^{25} +100.4^\circ$ (c = 0.225, CH_2Cl_2).

δH (CDCl_3) 7.62-7.57 (2H, m), 7.47-7.21 (13H, m), 5.54 (1H, d, J 8.1 Hz), 3.47 (3H, s), 3.03 (2H, t, J 7.8 Hz), and 2.73-2.67 (2H, m).

Anal. Calcd. for $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_2 \cdot 0.15\text{H}_2\text{O}$:

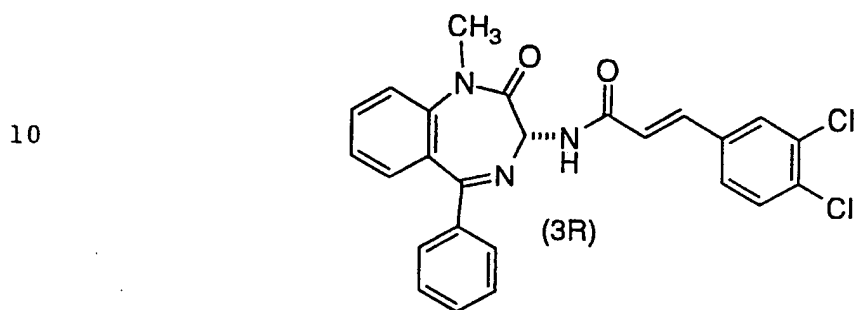
C, 75.04; H, 5.87; N, 10.50.

Found: C, 75.06; H, 5.78; N, 10.55%.

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Employing the procedure substantially as described above, but substituting an appropriate carboxylic acid for the 3-phenylpropanoic acid, the following compounds were prepared:

5

EXAMPLE 9

15

E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(3,4-dichlorophenyl)-2-propenamide

m.p. 145-147°C, $[\alpha]_D^{25} +77.8^\circ$ (c=0.126, CH₂Cl₂).

δ H (CDCl₃) 7.64-7.25 (14H, m), 6.61 (1H, d, J 15.6 Hz), 5.65 (1H, d, J 8.0 Hz), and 3.50 (3H, s).

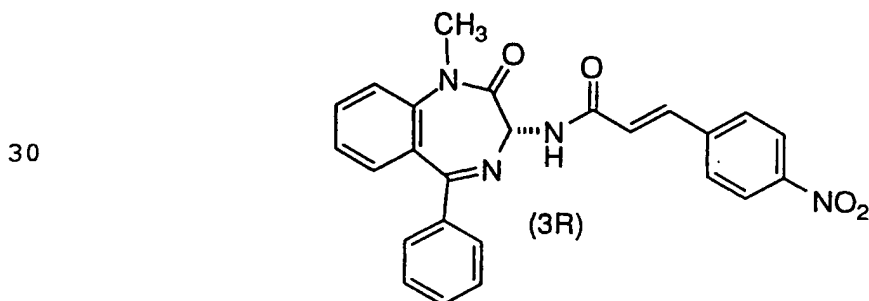
20

Anal. Calcd. for C₂₅H₁₉N₃O₂Cl₂:

C, 64.67; H, 4.12; N, 9.05.

Found: C, 64.57; H, 4.25; N, 9.01%.

25

EXAMPLE 10

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E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(4-nitrophenyl)-2-propenamide

m.p. 165-166 °C, $[\alpha]_D^{+80.5^\circ}$ (c=0.126, CH₂Cl₂).

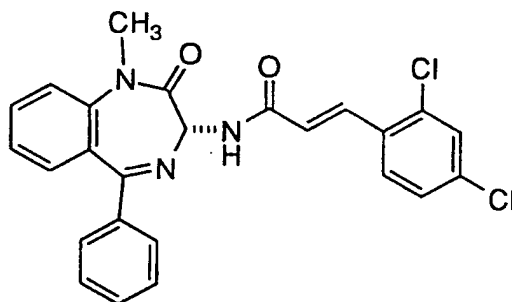
δ_H (CDCl₃) 8.26 (1H, d, J 8.8 Hz), 7.74-7.28 (13H, m), 6.76 (1H, d, J 15.6 Hz), 5.66 (1H, d, J 8.0 Hz), and 3.51 (3H, s).

Anal. Calcd. for C₂₅H₁₉N₄O₄:

C, 68.17; H, 4.58; N, 12.72.

Found: C, 68.25; H, 4.65; N, 12.57%.

EXAMPLE 11



E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)-2-propenamide

m.p. 137-139°C, $[\alpha]_D^{+66.0^\circ}$ (c=0.144, CH₂Cl₂).

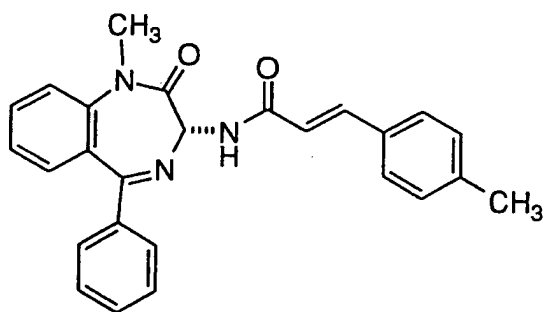
δ_H (CDCl₃) 8.02 (1H, d, J 15.6 Hz), 7.73-7.26 (13H, m), 6.66 (1H, d, J 15.6 Hz), 5.81 (1H, d, J 8.8 Hz), and 3.53 (3H, s).

Anal. Calcd. for C₂₅H₁₉Cl₂N₃O₂:

C, 64.67; H, 4.12; N, 9.05.

Found: C, 64.28; H, 4.24; N, 8.83%.

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EXAMPLE 12

E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-3-(4-methylphenyl)-2-propenamide

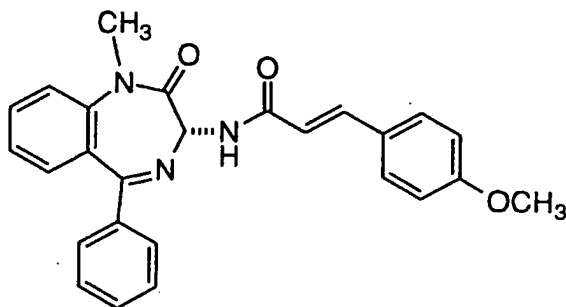
m.p. 133-135°C, $[\alpha]_D^{+90.4^\circ}$ (c=0.125, CH₂Cl₂).

δ_H (CDCl₃) 7.68-7.19 (15H, m), 6.59 (1H, d, J 15.6 Hz), 5.70 (1H, d, J 8.0 Hz), 3.50 (3H, s), and 2.38 (3H, s).

Anal. Calcd. for C₂₆H₂₃N₃O₂:

C, 76.26; H, 5.66; N, 10.26.

Found: C, 75.93; H, 5.82; N, 10.10%.

EXAMPLE 13

E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-3-(4-methoxyphenyl)-2-propenamide

m.p. 129-133°C, $[\alpha]_D^{+89.9^\circ}$ (c 0.188, CH₂Cl₂).

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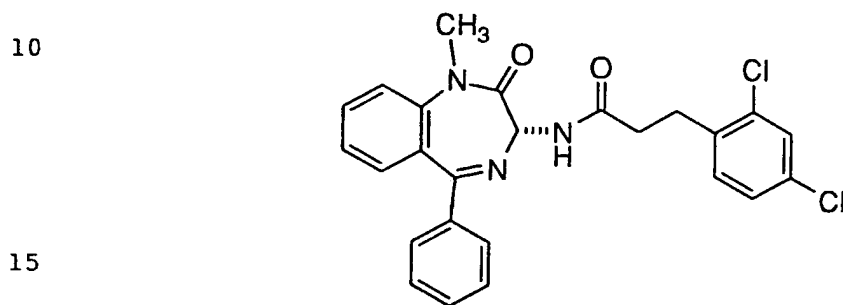
δ H (CDCl₃) 7.65-7.24 (14H, m), 6.92 (1H, d, J 8.8 Hz), 6.50 (1H, d, J 15.6 Hz), 5.69 (1H, d, J 8.0 Hz), 3.84 (3H, s), and 3.50 (3H, s)..

Anal. Calcd. for C₂₆H₂₃N₃O₃·0.30H₂O:

C, 72.48; H, 5.52; N, 9.75.

5 Found: C, 72.75; H, 5.60; N, 9.36%.

EXAMPLE 14



(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide

m.p. 92-95°C, [α]_D 90.5° (c = 0.196, CH₂Cl₂).

20 δ H (CDCl₃) 7.62-7.15 (13H, m), 5.52 (1H, d, J 8.1 Hz), 3.47 (3H, s), 3.10 (2H, t, J 7.6 Hz), and 2.68 (2H, dd, J 7.6, 2.8 Hz).

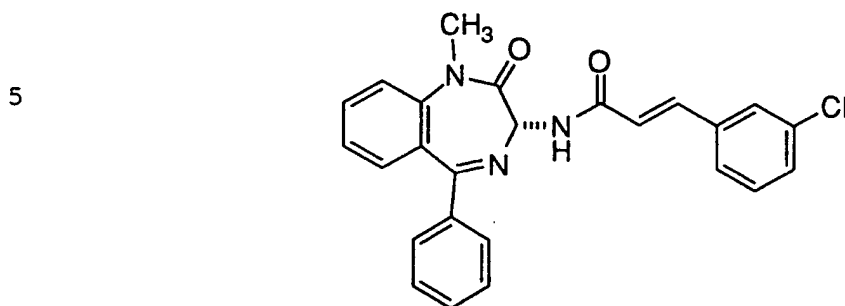
Anal. Calcd. for C₂₅H₂₁Cl₂N₃O₂·0.20H₂O:

C, 63.89; H, 4.59; N, 8.94.

25 Found: C, 63.86; H, 4.62; N, 8.87%.

30

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EXAMPLE 15

E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-3-(3-chlorophenyl)-2-propenamide

m.p. 229-231°C, $[\alpha]_D +86.2^\circ$ (c = 0.225, CH₂Cl₂).

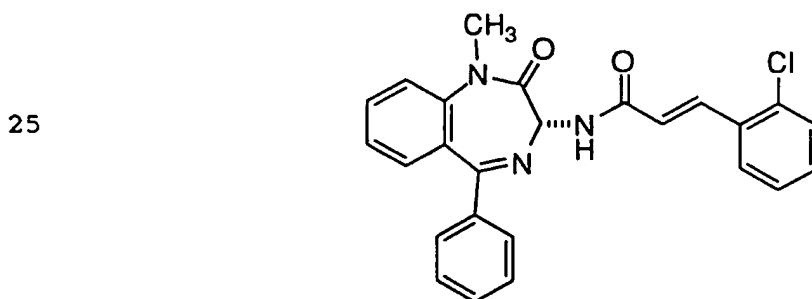
15 δ_H (CDCl₃) 7.64-7.26 (15H, m), 6.62 (1H, d, J 15.6 Hz), 5.66 (1H, d, J 8.1 Hz), and 3.50 (3H, s).

Anal. Calcd. for C₂₅H₂₀ClN₃O₂:

C, 69.85; H, 4.69; N, 9.77.

Found: C, 70.20; H, 4.83; N, 9.41%.

20

EXAMPLE 16

E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-3-(2-chlorophenyl)-2-propenamide

m.p. 128-131°C, $[\alpha]_D = +61.7^\circ$ (c = 0.196, CH₂Cl₂).

δ_H (CDCl₃) 8.06 (1H, d, J 15.6 Hz), 7.65-7.28 (14H, m), 6.62, (1H, d, J 15.6 Hz), 5.68 (1H, d, J 8.3 Hz), and 3.50 (3H, s).

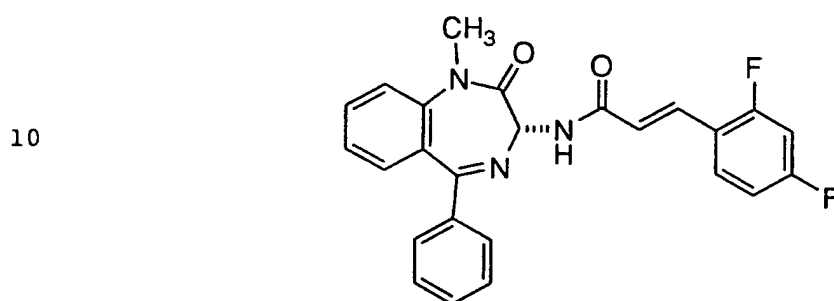
- 58 -

Anal. Calcd. for C₂₅H₂₀ClN₃O₂·0.20H₂O:

C, 69.27; H, 4.74; N, 9.69.

Found: C, 69.21; H, 4.68; N, 9.45%.

5 EXAMPLE 17



15 E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-3-(2,4-difluorophenyl)-2-propenamide
m.p. 121-123°C, [α]_D +76.8° (c = 0.111, CH₂Cl₂).

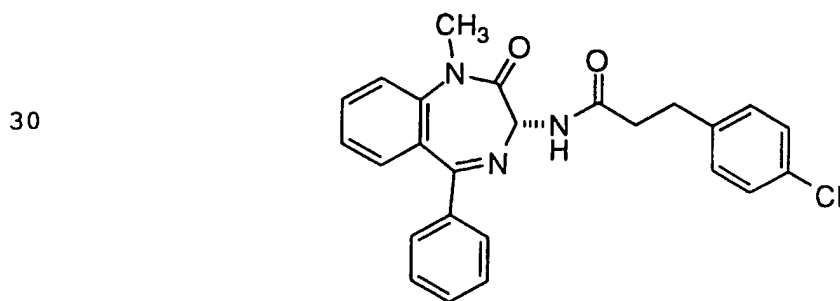
20 δ_H (CDCl₃) 7.71 (1H, d, J 15.9 Hz), 7.64-7.24 (11H, m), 6.92-6.84
(2H, m), 6.69 (1H, d, J 15.9 Hz), 5.67 (1H, d, J 8.1 Hz), and 3.50 (3H,
s).

Anal. Calcd. for C₂₅H₁₉F₂N₃O₂·0.10H₂O:

C, 69.31; H, 4.47; N, 9.70.

Found: C, 69.28; H, 4.57; N, 9.31%.

25 EXAMPLE 18



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(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(4-chlorophenyl)propanamide

m.p. 203-205°C, $[\alpha]_D^{25} +99.2^\circ$ (c = 0.300, CH₂Cl₂).

δ_H (CDCl₃) 7.62-7.16 (14H, m), 5.52 (1H, d, J 8.1 Hz), 3.47 (3H, s),

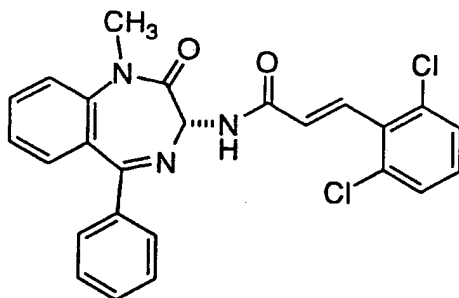
2.99 (2H, t, J 7.7 Hz), and 2.67 (2H, t, J 7.7 Hz).

Anal. Calcd. for C₂₅H₂₂ClN₃O₂:

C, 69.52; H, 5.13; N, 9.73.

Found: C, 69.50; H, 5.15; N, 9.72%.

EXAMPLE 19



E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,6-dichlorophenyl)-2-propenamide

m.p. 121-124°C, $[\alpha]_D^{25} +69.0^\circ$ (c = 0.342, CH₂Cl₂).

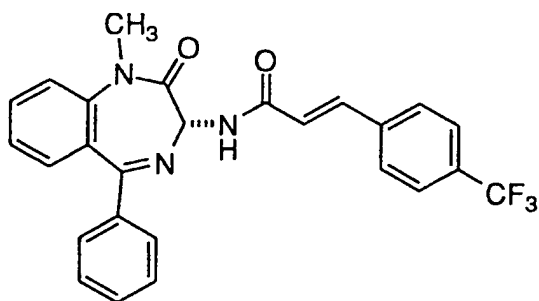
δ_H (CDCl₃) 7.79 (1H, d, J 16.1 Hz), 7.64-7.15 (13H, m), 6.78 (1H, d, J 15.8 Hz), 5.69 (1H, d, J 8.1 Hz), and 3.50 (3H, s).

Anal. Calcd. for C₂₅H₁₉Cl₂N₃O₂·0.15PhCH₃:

C, 65.44; H, 4.23; N, 8.79.

Found: C, 65.40; H, 4.38; N, 8.85%.

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EXAMPLE 20

E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-3-[4-(trifluoromethyl)phenyl]-2-propenamide

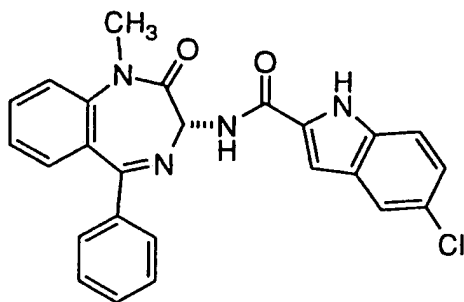
m.p. 133-137°C, $[\alpha]_D +68.7^\circ$ (c = 0.115, CH₂Cl₂).

δ_H (CDCl₃) 7.72-7.25 (15H, m), 6.71 (1H, d, J 15.6 Hz), 5.67 (1H, d, J
8.1 Hz), and 3.51 (3H, s).

Anal. Calcd. for C₂₆H₂₀F₃N₃O₂:

C, 67.38; H, 4.35; N, 9.07.

Found: C, 67.38; H, 4.45; N, 8.95%.

EXAMPLE 21

(+)-5-Chloro-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-
benzodiazepin-3-yl]indole-2-carboxamide

m.p. 160-164°C, $[\alpha]_D +103.8^\circ$ (c = 0.160, CH₂Cl₂).

δ_H (CDCl₃) 9.71 (1H, br s), 8.13 (1H, d, J 7.8 Hz), 7.68-7.09 (13H, m),
5.75 (1H, d, J 7.8 Hz), and 3.53 (3H, s).

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Anal. Calcd. for $C_{25}H_{19}ClN_4O_2 \cdot 0.25H_2O \cdot 0.15PhCH_3$:

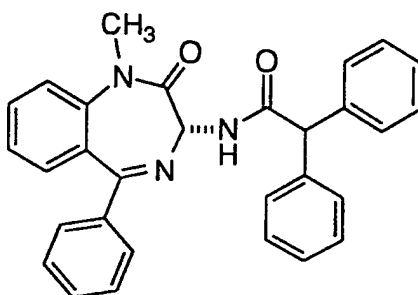
C, 67.84; H, 4.49; N, 12.15.

Found: C, 67.80; H, 4.41; N, 12.07%.

5

EXAMPLE 22

10



15 (+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-2,2-diphenylethanamide

m.p. 200-201°C, $[\alpha]_D^{+97.0^\circ}$ (c = 0.168, CH_2Cl_2).

δ_H ($CDCl_3$) 7.60-7.22 (20H, m), 5.58 (1H, d, J 8.1 Hz), 5.08 (1H, s),
and 3.44 (3H, s).

20 Anal. Calcd. for $C_{30}H_{25}N_3O_2 \cdot 0.15PhCH_3$:

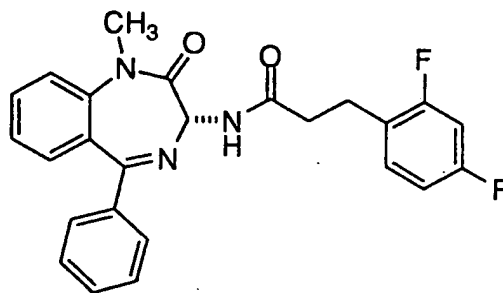
C, 78.79; H, 5.55; N, 8.88.

Found: C, 78.81; H, 5.63; N, 9.07%.

25

EXAMPLE 23

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- 62 -

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-3-(2,4-difluorophenyl)propanamide

m.p. 79-81°C, $[\alpha]_D^{+92.9^\circ}$ (c = 0.105, CH₂Cl₂).

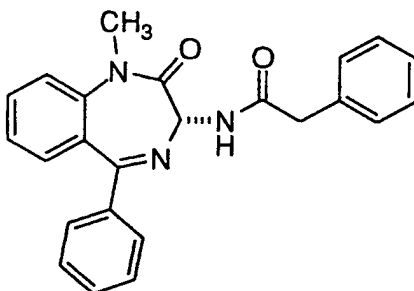
δ_H (CDCl₃) 7.62-7.56 (3H, m), 7.50-7.19 (8H, m), 6.82-6.76 (2H, m),
5.52 (1H, d, J 8.1 Hz), 3.47 (3H, s), 3.01 (2H, t, J 7.6 Hz), and 2.69
(2H, m).

Anal. Calcd. for C₂₅H₂₁F₂N₃O₂:

C, 69.27; H, 4.88; N, 9.69.

Found: C, 68.96; H, 4.99; N, 9.47%.

EXAMPLE 24



(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-2-phenylethanamide

m.p. 241-242°C (dec.), $[\alpha]_D^{+85.5^\circ}$ (c = 0.159, CH₂Cl₂).

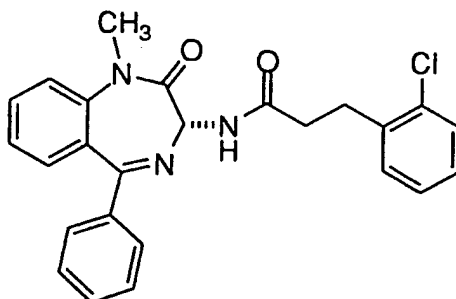
δ_H (CDCl₃) 7.59-7.55 (3H, m), 7.46-7.22 (12H, m), 5.51 (1H, d, J
8.1Hz), 3.72 (2H, s), and 3.44 (3H, s).

Anal. Calcd. for C₂₄H₂₁N₃O₂·0.55H₂O:

C, 73.28; H, 5.66; N, 10.68.

Found: C, 73.25; H, 5.38; N, 10.47%.

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EXAMPLE 25

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2-chlorophenyl)propanamide

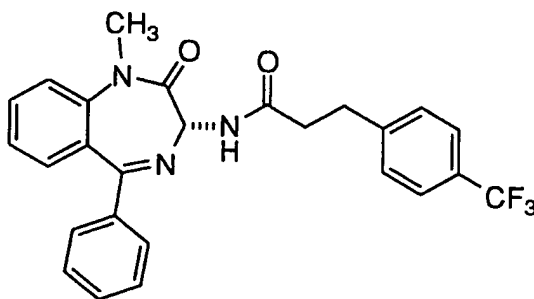
m.p. 158.5-159.5°C, $[\alpha]_D^{+95.8^\circ}$ (c = 0.224, CH₂Cl₂).

δ_H (CDCl₃) 7.62-7.57 (3H, m), 7.47-7.16 (11H, m), 5.55 (1H, d, J 8.1 Hz), 3.47 (3H, s), 3.14 (2H, t, J 7.9 Hz), and 2.75-2.69 (2H, m).

Anal. Calcd. for C₂₅H₂₂ClN₃O₂·0.15H₂O:

C, 69.09; H, 5.17; N, 9.67.

Found: C, 69.05; H, 5.12; N, 9.63%.

EXAMPLE 26

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-[4-(trifluoromethyl)phenyl]propanamide

m.p. 175-176°C, $[\alpha]_D^{+86.5^\circ}$ (c = 0.141, CH₂Cl₂).

δ_H (CDCl₃) 7.62-7.54 (5H, m), 7.47-7.22 (9H, m), 5.52 (1H, d, J 8.1 Hz), 3.47 (3H, m), 3.08 (2H, t, J 7.6 Hz), and 2.72 (2H, m).

- 64 -

Anal. Calcd. for $C_{26}H_{22}F_3N_3O_2 \cdot 0.80H_2O$:

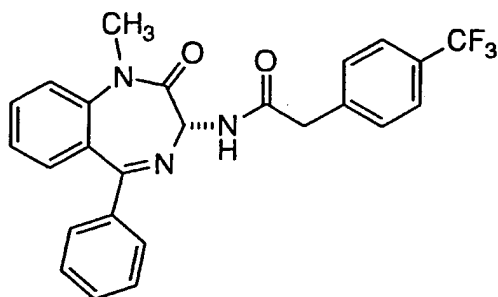
C, 65.08; H, 4.93; N, 8.76.

Found: C, 65.03; H, 4.63; N, 8.72%.

5

EXAMPLE 27

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(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-[4-(trifluoromethyl)phenyl]ethanamide

m.p. 224-226°C, $[\alpha]_D^{25} +68.0^\circ$ (c = 0.153, CH_2Cl_2). δ_H ($CDCl_3$) 7.63-7.55 (4H, m), 7.51-7.33 (8H, m), 7.26-7.23 (2H, m), 5.51 (1H, d, J 8.1 Hz), 3.77 (2H, s), and 3.46 (3H, s).

20

Anal. Calcd. for $C_{25}H_{20}F_3N_3O_2$:

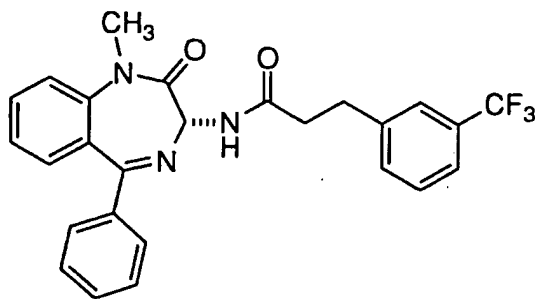
C, 66.51; H, 4.47; N, 9.31.

Found: C, 66.46; H, 4.36; N, 9.10%.

25

EXAMPLE 28

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- 65 -

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-[3-(trifluoromethyl)phenyl]propanamide

m.p. 135-136°C, $[\alpha]_D^{25} +78.8^\circ$ (c = 0.134, CH₂Cl₂).

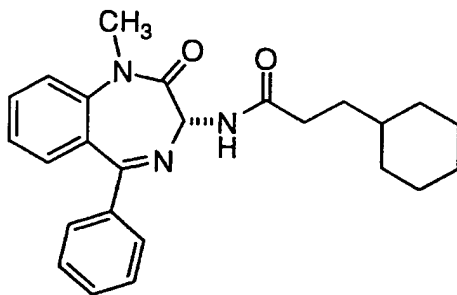
δ_H (CDCl₃) 7.62-7.56 (3H, m), 7.49-7.22 (11H, m), 5.53 (1H, d, J 8.1 Hz), 3.47 (3H, s), 3.08 (2H, t, J 7.3 Hz), and 2.72 (2H, m).

Anal. Calcd. for C₂₆H₂₂F₃N₃O₂:

C, 67.09; H, 4.76; N, 9.03.

Found: C, 67.03; H, 4.73; N, 9.13%.

EXAMPLE 29



(+)-3-Cyclohexyl-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]propanamide

m.p. 144.5-145.5°C, $[\alpha]_D^{25} +83.1^\circ$ (c = 0.116, CH₂Cl₂).

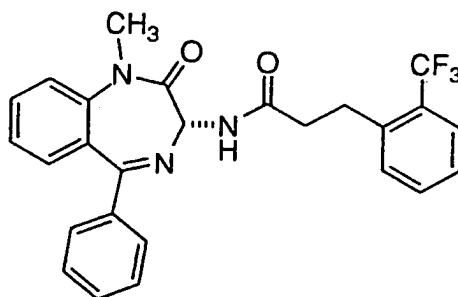
δ_H (CDCl₃) 7.62-7.56 (3H, m), 7.46-7.21 (7H, m), 5.55 (1H, d, J 8.3 Hz), 3.48 (3H, s), 2.41-2.36 (2H, m), 1.77-1.58 (7H, m), 1.31-1.16 (4H, m), and 0.98-0.90 (2H, m).

Anal. Calcd. for C₂₅H₂₉N₃O₂:

C, 74.41; H, 7.24; N, 10.41.

Found: C, 74.46; H, 7.27; N, 10.58%.

- 66 -

EXAMPLE 30

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-[2-(trifluoromethyl)phenyl]propanamide

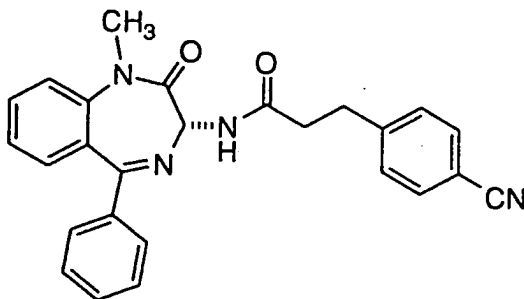
m.p. 110-113°C, $[\alpha]_D +79.2^\circ$ (c = 0.376, CH₂Cl₂).

δ_H (CDCl₃) 7.65-7.57 (4H, m), 7.50-7.22 (10H, m), 5.55 (1H, d, J 8.0 Hz), 3.47 (3H, s), 3.20 (2H, t, J 7.9 Hz), and 2.70 (2H, dt, J 7.9, 3.3 Hz).

Anal. Calcd. for C₂₆H₂₂F₃N₃O₂:

C, 67.09; H, 4.76; N, 9.03.

Found: C, 66.97; H, 4.76; N, 8.93%.

EXAMPLE 31

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(4-cyanophenyl)propanamide

m.p. 81-85°C, $[\alpha]_D +91.0^\circ$ (c = 0.111, CH₂Cl₂).

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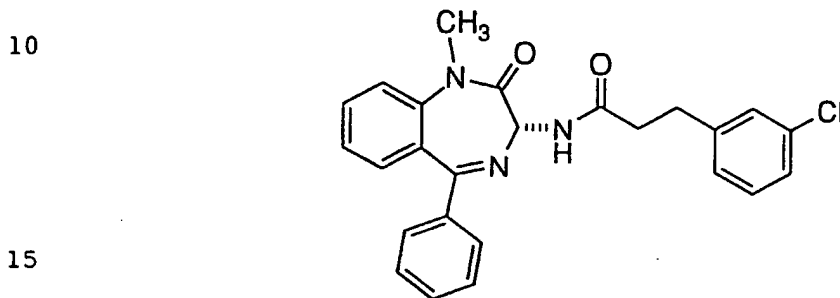
δ H (CDCl₃) 7.64-7.55 (4H, m), 7.48-7.16 (10H, m), 5.50 (1H, d, J 8.3 Hz), 3.47 (3H, s), 3.08 (2H, t, J 7.6 Hz), and 2.74-2.69 (2H, m).

Anal. Calcd. for C₂₆H₂₂N₄O₂·0.60H₂O·0.50PhCH₃:

C, 73.93; H, 5.62; N, 11.69.

5 Found: C, 73.98; H, 5.61; N, 11.71%.

EXAMPLE 32



(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(3-chlorophenyl)propanamide

m.p. 157-159°C, [α]_D +90.7° (c = 0.134, CH₂Cl₂).

20 δ H (CDCl₃) 7.62-7.57 (3H, m), 7.47-7.12 (11H, m), 5.53 (1H, d, J 8.1 Hz), 3.47 (3H, s), 3.00 (2H, t, J 7.3 Hz), and 2.71-2.66 (2H, m).

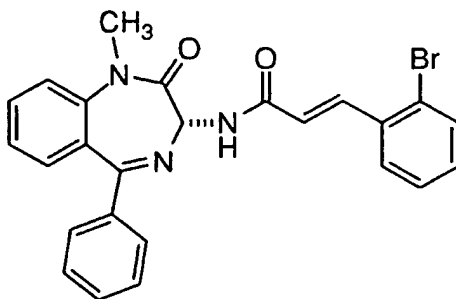
Anal. Calcd. for C₂₅H₂₂ClN₃O₂·0.55H₂O:

C, 67.96; H, 5.27; N, 9.51.

25 Found: C, 67.99; H, 5.18; N, 9.26%.

30

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EXAMPLE 33

E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2-bromophenyl)-2-propenamide

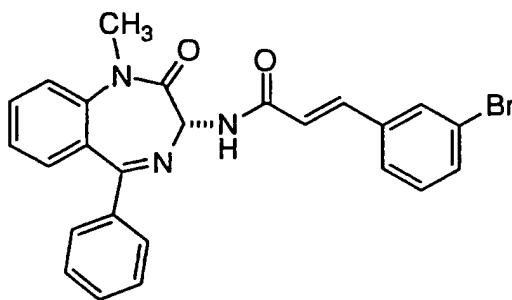
m.p. 113-116°C, $[\alpha]_D^{25} +44.2^\circ$ (c = 0.113, CH₂Cl₂).

δ_H (CDCl₃) 8.03 (1H, d, J 15.6 Hz), 7.64-7.16 (14H, m), 6.57 (1H, d, J 15.6 Hz), 5.68 (1H, d, J 8.1 Hz), and 3.50 (3H, s).

Anal. Calcd. for C₂₅H₂₀BrN₃O₂·0.60H₂O·0.30PhCH₃:

C, 63.48; H, 4.58; N, 8.19.

Found: C, 63.49; H, 4.38; N, 8.19%.

EXAMPLE 34

E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(3-bromophenyl)-2-propenamide

m.p. 221-223 d°C, $[\alpha]_D^{25} +65.5^\circ$ (c = 0.206, CH₂Cl₂).

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δ H (CDCl₃) 7.69 (1H, br s), 7.64-7.57 (4H, m), 7.51-7.37 (6H, m), 7.29-7.19 (4H, m), 6.62 (1H, d, J 15.6 Hz), 5.66 (1H, d, J 8.1 Hz), and 3.50 (3H, s).

Anal. Calcd. for C₂₅H₂₀BrN₃O₂·0.35H₂O·0.20PhCH₃:

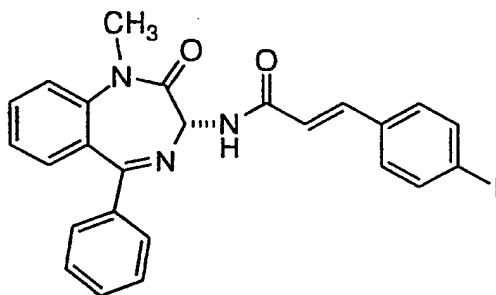
5 C, 63.54; H, 4.46; N, 8.42.

Found: C, 63.50; H, 4.39; N, 8.42%.

EXAMPLE 35

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E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(4-iodophenyl)-2-propenamide

20 m.p. 137-140°C, [α]_D +67.9° (c = 0.268, CH₂Cl₂).

δ H (CDCl₃) 7.75-7.72 (2H, m), 7.64-7.36 (8H, m), 7.29-7.16 (5H, m), 6.63 (1H, d, J 15.6 Hz), 5.66 (1H, d, J 8.1 Hz), and 3.50 (3H, m).

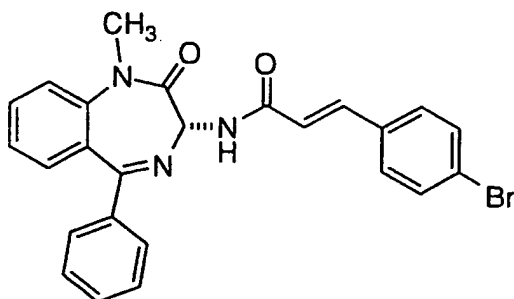
Anal. Calcd. for C₂₅H₂₀I₂N₃O₂·0.30PhCH₃:

25 C, 59.29; H, 4.06; N, 7.65.

Found: C, 59.29; H, 3.90; N, 7.40%.

30

- 70 -

EXAMPLE 36

E-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(4-bromophenyl)-2-propenamide

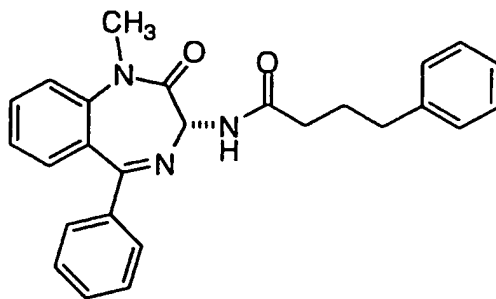
m.p. 121-124°C, $[\alpha]_D^{+75.6^\circ}$ (c = 0.201, CH₂Cl₂).

δ_H (CDCl₃) 7.64-7.57 (3H, m), 7.55-7.35 (11H, m), 7.28-7.24 (1H, m), 6.62 (1H, d, J 15.6 Hz), 5.66 (1H, d, J 8.1 Hz), and 3.50 (3H, s).

Anal. Calcd. for C₂₅H₂₀BrN₃O₂:

C, 63.30; H, 4.25; N, 8.86.

Found: C, 63.50; H, 4.20; N, 8.78%.

EXAMPLE 37

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-4-phenylbutanamide

m.p. 65-74°C, $[\alpha]_D^{+77.4^\circ}$ (c = 0.155, CH₂Cl₂).

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δ H (CDCl₃) 7.62-7.56 (3H, m), 7.46-7.19 (12H, m), 5.55 (1H, d, J 8.1 Hz), 3.47 (3H, s), 2.71 (2H, t, J 7.6 Hz), 2.42-2.37 (2H, m), and 2.09-2.01 (2H, m).

Anal. Calcd. for C₂₆H₂₅N₃O₂·0.30H₂O:

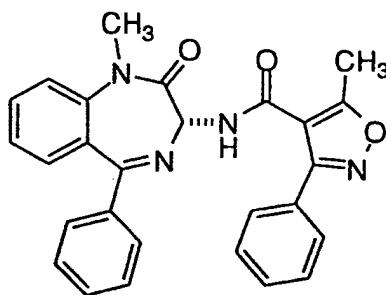
5 C, 74.91; H, 6.19; N, 10.08.

Found: C, 74.93; H, 6.05; N, 10.07%.

EXAMPLE 38

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15



(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-5-methyl-3-phenylisoxazole-4-carboxamide

20 m.p. 123-126°C, [α]_D +122.0° (c = 0.199, CH₂Cl₂).

δ H (CDCl₃) 7.79-7.76 (2H, m), 7.62-7.32 (11H, m), 7.26-7.21 (2H, m), 5.61 (1H, d, J 7.9 Hz), 3.42 (3H, s), and 2.76 (3H, s).

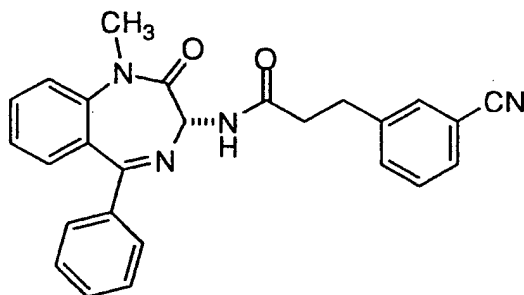
Anal. Calcd. for C₂₇H₂₂N₄O₃·0.40H₂O:

C, 70.85; H, 5.02; N, 12.24.

25 Found: C, 70.84; H, 4.91; N, 11.92%.

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EXAMPLE 39

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-3-(3-cyanophenyl)propanamide

m.p. 110-112°C, $[\alpha]_D^{+84.2^\circ}$ (c = 0.202, CH₂Cl₂).

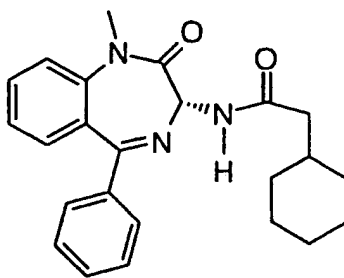
δ_H (CDCl₃) 7.63-7.22 (14H, m), 5.51 (1H, d, J 8.1 Hz), 3.47 (3H, s),

3.06 (2H, t, J 7.8 Hz), and 2.74-2.68 (2H, m).

Anal. Calcd. for C₂₆H₂₂N₄O₂·0.50H₂O:

C, 72.37; H, 5.37; N, 12.98.

Found: C, 72.52; H, 5.12; N, 12.59%.

EXAMPLE 40

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]cyclohexanethanamide

m.p. 144-146°C, $[\alpha]_D^{+72.1^\circ}$ (c=1.000, MeOH).

Anal. Calcd. for C₂₄H₂₇N₃O₂·0.20H₂O:

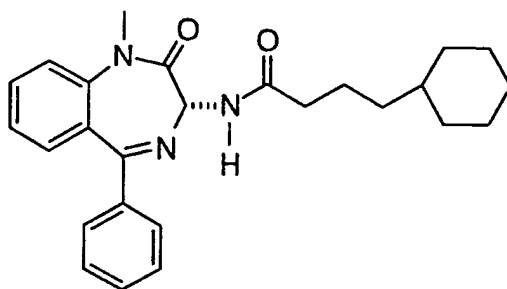
- 73 -

Found: C, 73.33; H, 7.03; N, 10.69.
C, 73.27; H, 7.02; N, 10.76%.

EXAMPLE 41

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15 (+)-4-Cyclohexyl-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]butanamide

[α]_D +57.7° (c=0.440, MeOH).

Anal. Calcd. for C₂₆H₃₁N₃O₂:

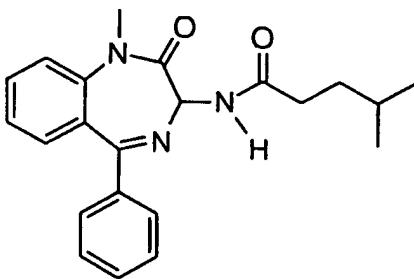
C, 74.79; H, 7.48; N, 10.06.

Found: C, 74.8; H, 7.78; N, 10.05%.

20

EXAMPLE 42

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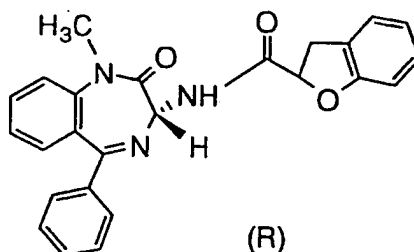
(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-4-methylpentanamide

m.p. 123-125°C, [α]_D +66.8° (c=0.500, MeOH).

Anal. Calcd. for C₂₂H₂₅N₃O₂·0.45H₂O:

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C, 71.12; H, 7.03; N, 11.31.
Found: C, 71.08; H, 6.81; N, 11.42%.

EXAMPLE 43

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2,3-dihydrobenzofuran-2-carboxamide

Diisopropylethylamine (0.3 mL, 223 mg, 1.72 mmol) was added to a stirred, cooled (0 °C) solution of 3(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (*J. Org. Chem.* 1987, 52, 3232-3239) (400 mg, 1.5 mmol), 2,3-dihydrobenzofuran-2-carboxylic acid (274 mg, 1.7 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (583 mg, 3.0 mmol), and 1-hydroxybenzotriazole (479 mg, 3.1 mmol) in DMF (4.5 mL). The mixture was stirred at room temperature for 18 h., poured into aqueous hydrochloric acid (3M, 12 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (20 mL) and brine (20 mL), dried (MgSO₄) and evaporated under reduced pressure. The residue was crystallized from 2-chloro-2-methylpropane/hexane to give (+)-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2,3-dihydrobenzofuran-2-carboxamide as a colorless solid (156 mg, 25%), m.p. 141-180°C, [α]_D +127.1° (c=0.425, CHCl₃). δ _H (CDCl₃) (3:1 Mixture of diastereoisomers) 8.44 (1H, m), 7.65-6.91 (13H, m), 5.52 (1H, m), 5.28 (1H, m), and 3.70-3.40 (5H, m). Anal. Calcd. for C₂₅H₂₁N₃O₃·0.25 Hexane

- 75 -

C, 73.50; H, 5.70; N, 9.71.

Found: C, 74.12; H, 5.57; N, 9.71%.

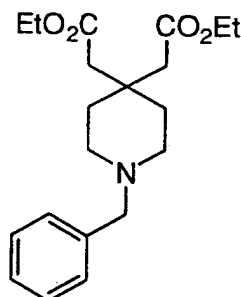
EXAMPLE 44

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(+)-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-1'-(1,1-dimethylethoxycarbonyl)spiro(cyclohexan-4,4'-piperidine)-1-carboxamide

10 Step A:

15

Diethyl 1-benzylpiperidine-4,4-diacetate

20

Ethanol (120 mL) was cooled in ice and ammonia bubbled through to give a saturated solution. 1-Benzyl-4-piperidone (40.0g, 211mmol) and ethyl cyanoacetate (47.8g, 423 mmol) were added, the reaction vessel stoppered and stored at 0°C overnight. The solid was collected, washed with ethanol and ether and dried in vacuo to give a yellow solid (68.86g). The solid (58.86g) was dissolved in a mixture of sulfuric acid (70 mL, 98%) and water (60 mL) and heated under reflux for three days the mixture cooled and most of the water evaporated. The residue was azeotroped with ethanol (4x750 mL), further ethanol (500 mL) added and the mixture heated under reflux for 20h, cooled in ice and sodium carbonate (100g) added slowly with vigorous stirring. The ethanol was evaporated under reduced pressure, water (800 mL) added and the mixture extracted with methylene chloride (3x400 mL). The combined organic extracts were dried (Na₂SO₄) and the solvent

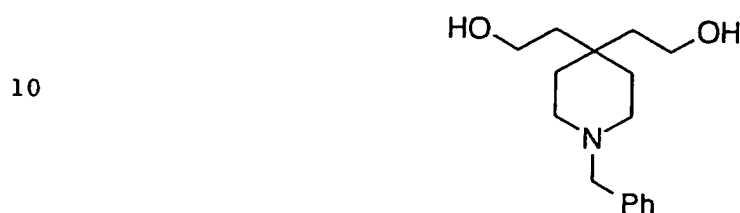
25
30

- 76 -

evaporated to give diethyl 1-benzylpiperidine-4,4-diacetate (37.51g). A small portion of this was purified by flash column chromatography.

NMR (300 MHz, CDCl₃) δ : 7.2-7.4 (m, 5H), 4.11 (q, J=7.3Hz, 4H), 3.50 (s, 2H), 2.56 (s, 4H), 2.4 (m, 4H), 1.7 (m, 4H), 1.24 (t, J=7.3Hz, 6H).

Step B:



1-Benzylpiperidine-4,4-diethanol

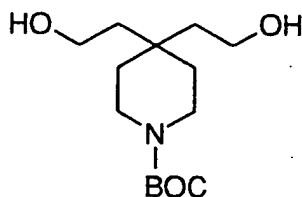
15 A solution of the diester (12.2 g, 35 mmol) in ether (25 mL) was added to a cooled (-30°C) and stirred suspension of LiAlH₄ (2.1 g, 55 mmol) in ether (400 mL), under argon. THF (60 mL) was added and the reaction mixture allowed to warm to room temperature. After recooling to 0°C, water (2.2 mL), 1M NaOH (4.4 mL) and water (5 mL) were added, the reaction mixture stirred vigorously for 30 min and the solid filtered off, washing well with ether. The combined filtrates were evaporated to afford a white solid which was triturated with ether to give 8 g of 1-benzylpiperidine-4,4-diethanol.

25 m.p. 75-78°C

NMR (300 MHz, CDCl₃) δ : 7.2-7.4 (m, 5H), 3.7 (t, J = 6.8 Hz, 4H), 3.52 (s, 2H), 2.7 (brs, 2H), 2.43 (m, 4H), 1.66 (t, J = 6.8 Hz, 4H), 1.5 (m, 4H).

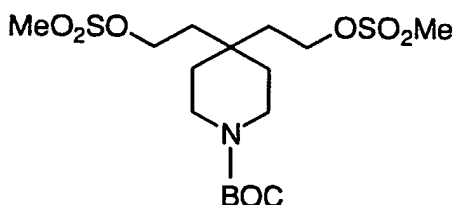
30

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Step C:1-t-Butoxycarbonylpiperidine-4,4-diethanol

The benzylamine (2.07 g, 7.9 mmol) was dissolved in methanol (60 mL), BOC₂O (1.72 g, 7.9 mmol) added and the mixture hydrogenated at 50 psi over 10% palladium hydroxide on charcoal (200 mg) for 18 hours. The reaction mixture was filtered through celite, washed with methanol and the filtrate evaporated to give 1-t-butoxycarbonylpiperidine-4,4-diethanol (2.0 g).

NMR (300 MHz, CDCl₃) δ : 3.7 (m, 4H), d 3.3 (m, 6H), 1.65 (t, J = 6.8 Hz, 4H), 1.41 (s, 9H).

Step D:1-t-Butoxycarbonylpiperidine-4,4-diethanol, bis(methanesulfonate)

The diol (2.41 g, 8.9 mmol) was dissolved in dichloromethane (50 mL), the solution cooled to -20°C under argon before addition of triethylamine (3.7 mL, 26 mmol) and methanesulfonyl chloride (1.6 mL, 20 mmol). After 30 min., the reaction mixture was poured into ice cold 10% citric acid and extracted with ether (X3). The combined extracts were washed with water, saturated NaHCO₃ and brine, dried (MgSO₄) and the solvent evaporated to afford 1-t-butoxycarbonylpiperidine-4,4-diethanol, bis(methanesulfonate) (3.2g).

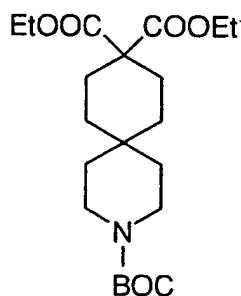
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NMR (300 MHz, CDCl₃) δ : 4.32 (t, J = 7.1 Hz, 4H), 3.4 (m, 4H), 3.04 (s, 6H), 1.89 (t, J = 7.1 Hz, 4H).

Step E:

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10



Diethyl 3-t-butyloxycarbonyl-3-azaspiro[5.5]undecane-9,9-dicarboxylate

To a slurry of 60% NaH (2.04 g, 0.51 mole) in toluene
15 (160 mL), under argon, was slowly added diethyl malonate (3.72 mL, 24.3 mmol). The mixture was cooled to 0°C and the bis-mesylate 1 (7.0 g, 16.3 mmol) added as a solid and the mixture heated to reflux for 18 hours. The reaction was quenched into 10% citric acid (100 mL) and the product extracted with CH₂Cl₂ (2x150 mL). The extracts were
20 dried (Na₂SO₄), concentrated to an oil, and chromatographed on silica to give 3.83 g (60%) of diethyl 3-t-butyloxycarbonyl-3-azaspiro-[5.5]undecane-9,9-dicarboxylate.

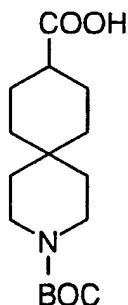
¹H NMR (CDCl₃) δ : 1.22 (t, 6H), 1.4 (s, 9H), 2.0 (m, 4H), 3.35 (m,
25 4H), 4.2 (q, 4H).

30

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Step F:

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10 3-t-Butyloxycarbonyl-3-azaspiro[5.5]undecane-9-carboxylic acid

To a solution of the diester 2 (3.69 g, 0.0093 m) in THF (50 mL) was added 1N LiOH (47 mL). The reaction was stirred for 3 days at 25°C, diluted with water (50 mL) and pH adjusted to 2.2 with KHSO₄. The product was extracted into ethyl acetate (2x75 mL), dried
15 (Na₂SO₄), and concentrated to a foam (3.5 g). The solid was melted in a flask at 140°C for 2 hours, cooled and the oil dissolved in THF (15 mL), 1N LiOH (10 mL) added and mixture stirred overnight at 30°C. The reaction was concentrated to remove THF, diluted with water (20 mL) and washed with diethyl ether (10 mL). The pH was adjusted to
20 2.5 with KHSO₄ and product extracted (3x50 mL) with ethyl acetate. The extracts were dried (Na₂SO₄), filtered and concentrated to yield 3-t-butylloxycarbonyl-3-azaspiro[5.5]undecane-9-carboxylic acid as a foam (2.48 g, 90%).

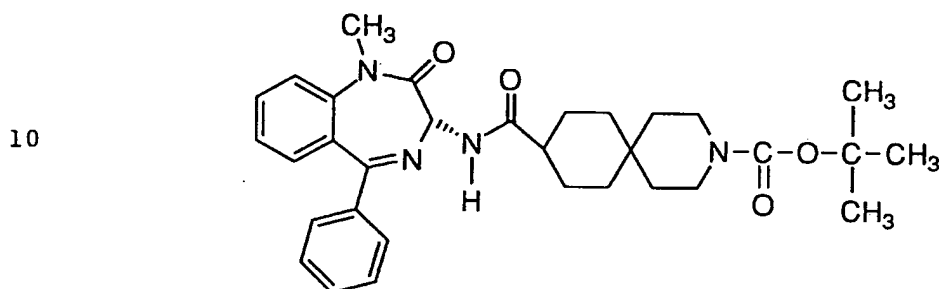
25 ¹H NMR (CDCl₃, partial) δ: 1.45 (s, 9H), 3.4 (m, 4H).

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Employing the procedure substantially as described in Example 43 but substituting an appropriate acid for the 2,3-dihydrobenzofuran-2-carboxylic acid, the following compounds were prepared:

5 Step G:



15 (+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-1'-(1,1-dimethylethoxycarbonyl)spiro(cyclohexan-4,4'-piperidine)-1-carboxamide

m.p. 135-138°C, $[\alpha]_D^{25} +58.8^\circ$ (C=0.925, CHCl₃).

20 δ_H (CDCl₃) 7.61-7.23 (10H, m), 5.54 (1H, d, J 9.0 Hz), 3.47 (3H, s), 3.37 (4H, m), 2.28 (1H, m), and 1.81-1.18 (21H, s).

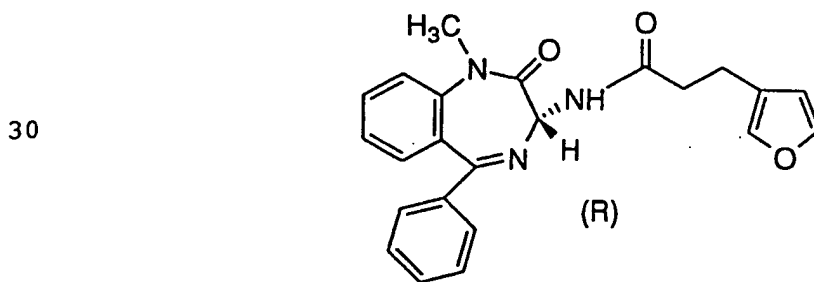
Anal. Calcd. for C₃₂H₄₀N₄O₄:

C, 70.56; H, 7.40; N, 10.29.

Found: C, 70.21; H, 7.40; N, 10.16%.

25

EXAMPLE 45



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(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-diazepin-3-yl]-3-(furan-2-yl)propanamide

m.p. 115-118°C, $[\alpha]_D^{25} +65.8^\circ$ (c=0.800, CHCl₃).

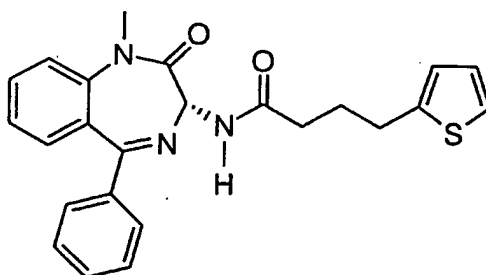
δ_H (CDCl₃) 7.62-7.26 (11H, m), 6.28 (1H, dd, J 3.2, 2.0 Hz), 6.08 (1H, dd, J 3.2, 0.7 Hz), 5.58 (1H, d, J 8.1 Hz), 3.48 (3H, s), 3.04 (2H, t, J 7.6 Hz), and 2.75 (2H, m).

Anal. Calcd. for C₂₃H₂₁N₃O₃·0.3Hexane:

C, 72.07; H, 6.15; N, 10.17.

Found: C, 71.78; H, 6.30; N, 9.77%.

EXAMPLE 46



(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-4-(2-thienyl)butanamide

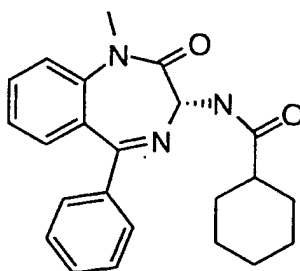
m.p. 170-180°C, $[\alpha]_D^{25} +63.5^\circ$ (c=1.000, MeOH).

Anal. Calcd. for C₂₄H₂₃N₃O₂S·0.95H₂O:

C, 66.32; H, 5.77; N, 9.67.

Found: C, 66.32; H, 5.34; N, 9.40%.

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EXAMPLE 47

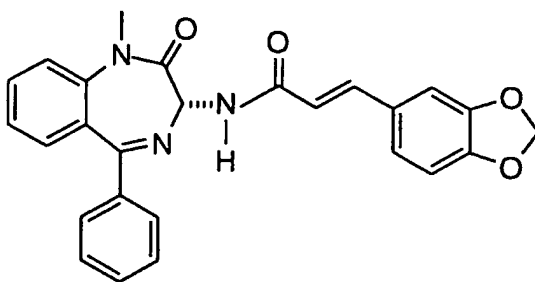
(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]cyclohexylcarboxamide

m.p. 213-214°C, $[\alpha]_D^{+62.4}$ (c=1.000, MeOH).

Anal. Calcd. for C₂₃H₂₄N₃O₂:

C, 73.77; H, 6.46; N, 11.22.

Found: C, 73.86; H, 6.81; N, 11.15%.

EXAMPLE 48

(E)-(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(3,4-methylenedioxyphenyl)-2-propenamide

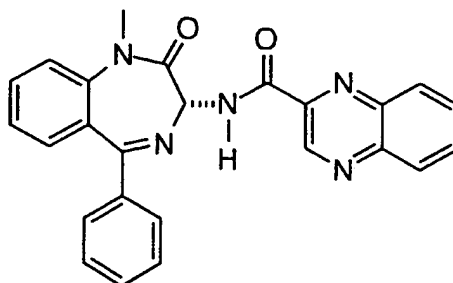
m.p. 143-145°C, $[\alpha]_D^{+62.3}$ (c=0.960, MeOH).

Anal. Calcd. for C₂₅H₂₁N₃O₄·0.10H₂O·0.20Et₂O:

C, 69.78; H, 5.27; N, 9.46.

Found: C, 69.78; H, 4.98; N, 9.28%.

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EXAMPLE 49

(+)-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-quinoxalinecarboxamide

$[\alpha]_D^{+85.8^\circ}$ (c=0.360, MeOH).

Anal. Calcd. for C₂₅H₁₉N₅O₂:

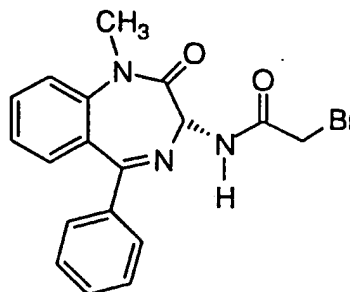
C, 69.96; H, 4.90; N, 15.33.

Found: C, 69.95; H, 4.72; N, 15.25%.

EXAMPLE 50

(+)-N-[(3R)-2,3-Dihydro-2-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-(phenylamino)acetamide

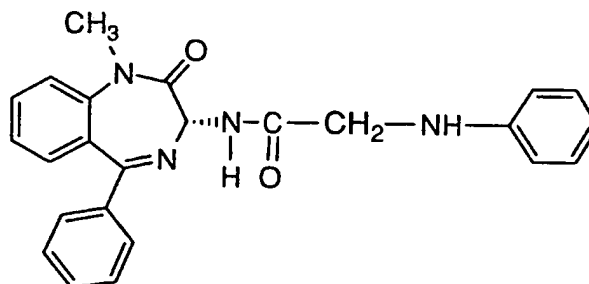
Step A:



N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-bromoacetamide

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Bromoacetyl bromide (165 μ L, 383 mg, 1.9 mmol) was added to an ice cooled solution of 3(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (*J. Org. Chem.* 1987, 52, 3232-3239) (500 mg, 1.88 mmol) and triethylamine (264 μ L, 192 mg, 1.9 mmol) in methylene chloride (10 mL) and the mixture was stirred at room temperature for 1 h. The mixture was washed with water (3 x 10 mL), dried (MgSO_4) and the solvent was evaporated under reduced pressure to give N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-bromoacetamide as a colorless foam (760 mg, 100%).
 δ H (CDCl_3) 8.24 (1H, d, J 7.8 Hz), 7.64-7.24 (9H, m), 5.48 (1H, d, J 7.8 Hz), 4.00 (2H, m), and 3.50 (3H, s).

Step B:

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-(phenylamino)acetamide

Aniline (297 μ L, 304 mg, 3.26 mmol) was added to a solution of N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-bromoacetamide (600 mg, 1.55 mmol) in ethanol (25 mL) and the mixture was heated under reflux for 24 h. The mixture was cooled and the solid was collected and recrystallized from ethanol (20 mL) to give (+)-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-(phenylamino)acetamide as a colorless solid (500 mg, 81%), m.p. 245-246°C, $[\alpha]_D +119^\circ$ (C=0.850, CHCl_3).

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δ H (CDCl₃) 8.26 (1H, d, J 8.3 Hz), 7.63-7.20 (12H, m), 6.81 (1H, t, J 7.3 Hz), 6.72 (2H, d, J 7.6 Hz), 5.56 (1H, d, J 8.3 Hz), 3.95 (2H, d, J 1.5 Hz), and 3.45 (3H, s).

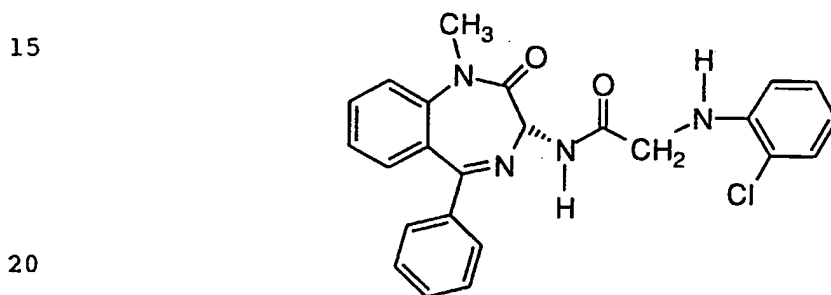
Anal. Calcd. for C₂₄H₂₂N₄O₂:

5 C, 72.34; H, 5.57; N, 14.06.

Found: C, 72.37; H, 5.59; N, 14.32%.

Employing the procedure substantially as described above,
but substituting 2-chloroaniline or 4-(trifluoromethyl)aniline for the
10 aniline, the following compounds were prepared:

EXAMPLE 51



(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-
diazepin-3-yl]-2-(2-chlorophenylamino)acetamide

m.p. 222-224°C, [α]_D +111° (c=0.973, CHCl₃).

25 δ H (CDCl₃) 8.15 (1H, d, J 8.3 Hz), 7.60-7.16 (12H, m), 6.71 (2H, m),
5.57 (1H, d, J 8.3 Hz), 4.01 (2H, d, J 2.7 Hz), and 3.45 (3H, s).

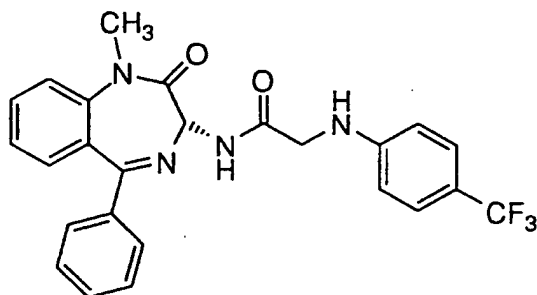
Anal. Calcd. for C₂₄H₂₁ClN₄O₂:

C, 66.59; H, 4.89; N, 12.94.

Found: C, 66.40; H, 4.94; N, 12.92%.

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EXAMPLE 52

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-[4-(trifluoromethyl)phenylamino]acetamide

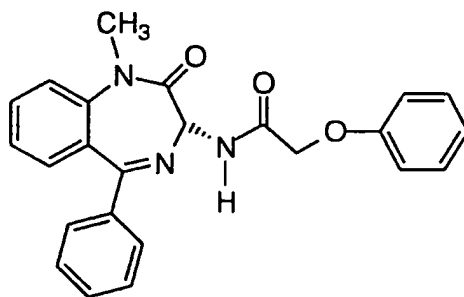
m.p. 218-219°C, $[\alpha]_D^{+91.9^\circ}$ (c = 0.419, CHCl₃).

δ_H (CDCl₃) 8.13 (1H, d, J 9.0 Hz), 7.70-7.25 (12H, m), 6.72 (2H, d, J 8.7 Hz), 5.60 (1H, d, J 9.0 Hz), 4.05 (2H, m), and 3.50 (3H, s).

Anal. Calcd. for C₂₅H₂₁F₃N₄O₂·0.7H₂O:

C, 62.68; H, 4.71; N, 11.69.

Found: C, 62.47; H, 4.32; N, 11.44%.

EXAMPLE 53

(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-(phenoxy)acetamide

Phenol (104 mg, 1.1 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 44 mg, 1.1 mmol) in toluene (10 mL). When hydrogen evolution had stopped, N-[(3R)-2,3-

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5 dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-bromoacetamide (400 mg, 1.04 mmol) was added and the mixture was stirred at room temperature for 18 h. The mixture was washed with water (3 x 15 mL), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was triturated with 2-propanol and the solid was collected and recrystallized from 2-propanol (5 mL) to give (+)-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-(phenoxy)acetamide as a colorless solid (112 mg, 27%), m.p. 126-128°C, [α]_D +81.6 (C=0.692, CHCl₃).
10 δ H (CDCl₃) 8.49 (1H, d, J 8.2 Hz), 7.64-7.01 (14H, m), 5.61 (1H, d, J 8.2 Hz), 4.65 (1H, d, J 14.6 Hz), 4.58 (1H, d, J 14.6 Hz), and 3.50 (3H, s).

Anal. Calcd. for C₂₄H₂₁N₃O₃:

C, 72.17; H, 5.30; N, 10.52.

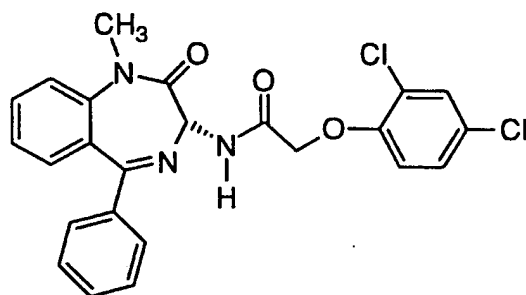
15 Found: C, 71.84; H, 5.25; N, 10.41%.

Employing the procedure substantially as described above, but substituting 2,4-dichlorophenol, thiophenol or 2,4-dichlorothiophenol for the phenol, the following compounds were prepared:

20

EXAMPLE 54

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(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-(2,4-dichlorophenoxy)acetamide
m.p. 206°C, [α]_D +31.1° (c=0.289, CHCl₃).

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δ H (CDCl₃) 8.75 (1H, d, J 9.0 Hz), 7.65-7.20 (11H, m), 6.90 (1H, d, J 8.7 Hz), 5.60 (1H, d, J 9.0 Hz), 4.65 (2H, m), and 3.50 (3H, s).

Anal. Calcd. for C₂₄H₁₉Cl₂N₃O₃·0.3H₂O:

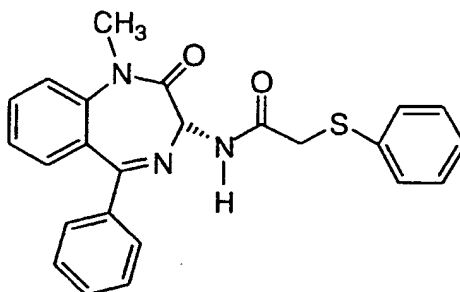
C, 60.85; H, 4.17; N, 8.87.

5 Found: C, 60.80; H, 4.04; N, 8.87%.

EXAMPLE 55

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15



(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-diazepin-3-yl]-2-(phenylthio)acetamide

[α]_D +104.9° (c=0.316, CHCl₃).

20 δ H (CDCl₃) 8.50 (1H, d, J 9.0 Hz), 7.60-7.20 (14H, m), 5.50 (1H, d, J 9.0 Hz), 3.75 (2H, m), and 3.45 (3H, s).

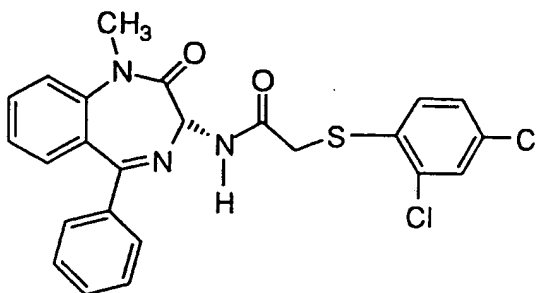
Anal. Calcd. for C₂₄H₂₁N₃O₂S:

C, 69.37; H, 5.10; N, 10.11.

25 Found: C, 68.98; H, 5.06; N, 9.76%.

EXAMPLE 56

30



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(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-2-(2,4-dichlorophenylthio)acetamide

$[\alpha]_D^{+97.4^\circ}$ (c=0.286, CHCl₃).

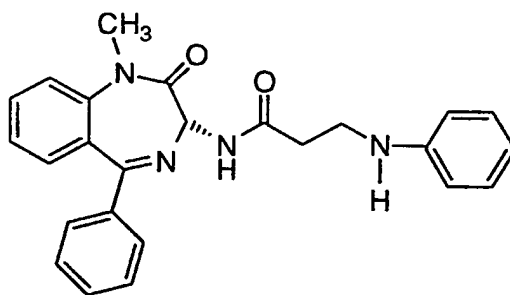
δ_H (CDCl₃) 8.35 (1H, d, J 9.0 Hz), 7.70-7.20 (12H, m), 5.50 (1H, d, J 9.0 Hz), 3.70 (2H, m), and 3.50 (3H, s).

Anal. Calcd. for C₂₄H₁₉Cl₂N₃O₂S:

C, 59.51; H, 3.95; N, 8.67.

Found: C, 59.32; H, 3.95; N, 8.65%.

EXAMPLE 57



(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(phenylamino)propanamide

3-Bromopropionyl chloride (2.01 mL, 3.428 g, 20 mmol) was added to an ice cooled solution of 3(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (*J. Org. Chem.* 1987, 52, 3232-3239) (5.0 g, 18.8 mmol) and triethylamine (2.79 mL, 2.02 mg, 20 mmol) in methylene chloride (85mL) and the mixture was stirred at room temperature for 18 h. The mixture was washed with saturated aqueous sodium hydrogen carbonate (85 mL), water (2 x 85 mL), and brine (85 mL), dried (MgSO₄) and the solvent was evaporated under reduced pressure. A sample (0.5 g, 1.25 mmol) was dissolved in ethanol (25 mL), aniline (230 μ L, 233 mg, 2.5 mmol) was added and the mixture was heated under reflux for 70 h. The mixture was cooled and the solid was collected and recrystallized from ethanol to give (+)-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-

- 90 -

yl]-3-(phenylamino)propanamide as a colorless solid, m.p. 218-221°C, $[\alpha]_D +58.2^\circ$ ($c=0.585$, CHCl_3).

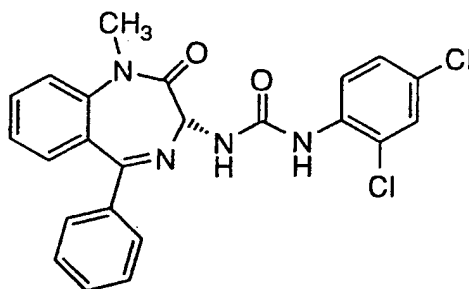
δ_H (CDCl_3) 7.60-6.71 (16H, m), 5.54 (1H, d, J 8.1 Hz), 3.54 (2H, t, J 6.1 Hz), 3.52 (3H, s), and 2.70 (2H, m).

5 Anal. Calcd. for $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_2 \cdot 0.5\text{EtOH}$:

C, 71.70; H, 6.25; N, 12.87.

Found: C, 71.42; H, 5.98; N, 12.84%.

EXAMPLE 58



15
20 (+)-1-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)urea

2,4-Dichlorophenylisocyanate (188 mg, 1.0 mmol) was added to a solution of 3(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (*J. Org. Chem.* 1987, 52, 3232-3239) (265 mg, 1.0 mmol) in tetrahydrofuran (20 mL). The mixture was stirred at
25 room temperature for 18 h. and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (99.5:0.5) and the residue was crystallized from CH_2Cl_2 /hexane to give (+)-1-
30 [(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)urea as a colorless solid, m.p. 215-216.5°C, $[\alpha]_D +76.2^\circ$ ($c=0.261$, CHCl_3).

δ_H (CDCl_3) 8.10 (1H, d, J 9.0 Hz), 7.65-6.95 (13H, m), 5.50 (1H, d, J 9.0 Hz), and 3.50 (3H, s).

Anal. Calcd. for $\text{C}_{23}\text{H}_{18}\text{Cl}_2\text{N}_4\text{O}_2 \cdot 0.3\text{H}_2\text{O}$:

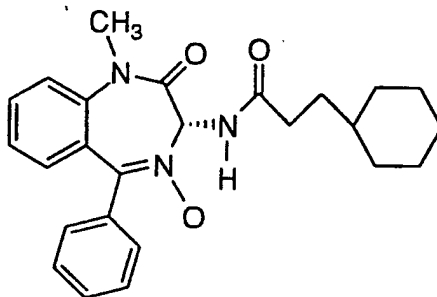
- 91 -

Found: C, 60.22; H, 4.09; N, 12.21.
C, 60.28; H, 3.89; N, 12.10%.

EXAMPLE 59

5

10



15 (-)-3-Cyclohexyl-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-4-oxido-5-phenyl-1H-1,4-benzodiazepin-3-yl]propanamide

3-Chloroperoxybenzoic acid (80%, 0.32 g, 1.5 mmol) was added to a solution of (+)-3-cyclohexyl-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]propanamide (0.60 g, 1.5 mmol) in dichloromethane (25 mL) and the mixture was stirred at room temperature for 18 h. Further 3-chloroperoxybenzoic acid (80%, 0.1 g, 0.5 mmol) was added and the mixture was stirred for 24 h. The mixture was washed with saturated aqueous sodium hydrogen carbonate (4 x 25 mL), water (2 x 25 mL) and brine (25 mL), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was recrystallized from toluene/hexane (65:35) to give (-)-3-cyclohexyl-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-4-oxido-5-phenyl-1H-1,4-benzodiazepin-3-yl]propanamide as colorless prisms, m.p. 222-224°C, [α]_D -80.7° (c=1.15, CHCl₃).

30 δ H (CDCl₃) 7.71-7.23 (10H, m), 6.01 (1H, d, J 9.3 Hz), 3.54 (3H, s), 2.48 (2H, m), and 1.76-0.89 (13H, m).

Anal. Calcd. for C₂₅H₂₉N₃O₃·0.5H₂O:

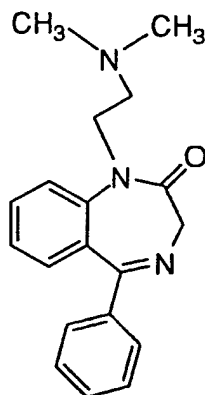
C, 70.06; H, 7.06; N, 9.81.

Found: C, 70.10; H, 6.80; N, 9.79%.

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EXAMPLE 60

N-[2,3-Dihydro-1-(2-dimethylaminoethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide

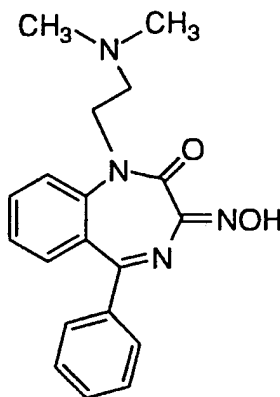
Step A:

2,3-Dihydro-1-(2-dimethylaminoethyl)-5-phenyl-1H-1,4-benzodiazepin-2-one

2,3-Dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one (1.00 g, 4.23 mmol) was added to hexane washed sodium hydride (60% dispersion in mineral oil, 186 mg, 4.65 mmol) in DMF (5 mL). Further DMF (10 mL) was added and the mixture was stirred at room temperature. 2-(Dimethylamino)ethyl chloride hydrochloride (0.73 g, 5 mmol) was added to hexane washed sodium hydride (60% dispersion in mineral oil, 200 mg, 5.0 mmol) in DMF (5 mL) and the mixtures were combined. Potassium iodide (1 crystal) was added and the mixture was stirred at 110°C for 30 min. The solvent was evaporated under reduced pressure, water was added and the mixture was extracted with ethyl acetate. The combined organic fractions were washed with water (2 x), dried (MgSO₄) and the solvent was evaporated under reduced pressure to give 2,3-dihydro-1-(2-dimethylaminoethyl)-5-phenyl-1H-1,4-benzodiazepin-2-one (1.21 g, 93%).

δ H (CDCl₃) 7.63-7.16 (9H, m), 4.77 (1H, d, J 10.6 Hz), 4.41 (1H, m), 3.80 (1H, m), 3.78 (1H, d, J 10.6 Hz), 2.49 (2H, m), and 2.13 (6H, s).

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Step B:2,3-Dihydro-1-(2-dimethylaminoethyl)-3-hydroxyimino-5-phenyl-1H-1,4-benzodiazepin-2-one

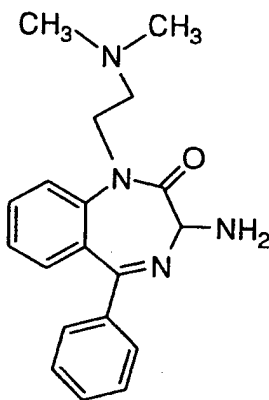
2,3-Dihydro-1-(2-dimethylaminoethyl)-5-phenyl-1H-1,4-benzodiazepin-2-one (1.21 g, 3.9 mmol) was dissolved in toluene (20 mL). The mixture was cooled to -78 °C and potassium *t*-butoxide (1.0M solution in *t*-butanol, 4.72 mL, 4.72 mmol) was added. The mixture was stirred at -78 °C for 20 min., then isoamyl nitrite (0.63 mL, 0.55 g, 4.72 mmol) was added. The mixture was stirred at -78°C for 90 min. then allowed to warm to room temperature and poured into aqueous citric acid (1M, 10 mL). The pH was adjusted to 5.0 with aqueous sodium hydroxide then to 7.0 with saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate (50 mL) and the organic layer was aged at room temperature. The solid which formed was collected and dried in vacuo to give 2,3-dihydro-1-(2-dimethylaminoethyl)-3-hydroxyimino-5-phenyl-1H-1,4-benzodiazepin-2-one (0.876 g, 66%) as a solid, m.p. 232-234°C. δ_{H} (d₆-DMSO) 10.90 (1H, s), 7.72-7.25 (9H, m), 4.40 (1H, m), 3.80 (1H, m), 2.50 (2H, m), and 1.85 (6H, s).

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Step C:

5

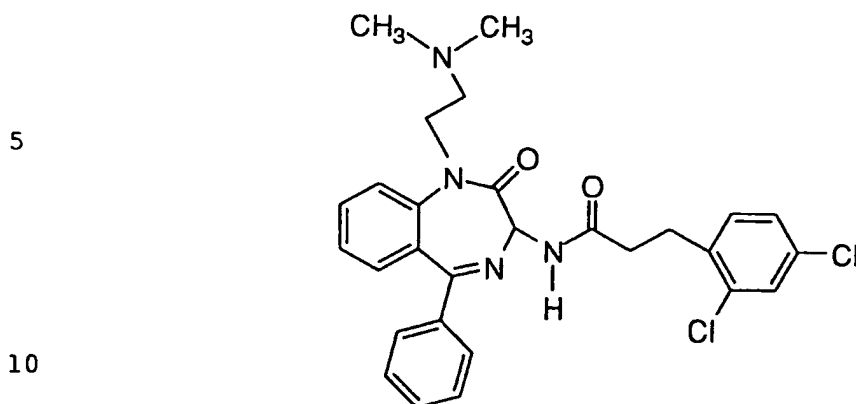
10

3-Amino-2,3-dihydro-1-(2-dimethylaminoethyl)-5-phenyl-1H-1,4-benzodiazepin-2-one

15 Ethyl isocyanate (320 μ L, 287 mg, 4.0 mmol) was added to a mixture of 2,3-dihydro-1-(2-dimethylaminoethyl)-3-hydroxyimino-5-phenyl-1H-1,4-benzodiazepin-2-one (0.91 g, 2.7 mmol) and triethylamine (0.56 mL, 0.41 g, 4.0 mmol) in THF (30 mL). The mixture was heated under reflux for 7 h., further ethyl isocyanate (167 μ L, 150 mg, 2.1 mmol) was added and the mixture was heated under reflux for 12 h. The mixture was cooled, the solvent was evaporated under reduced pressure and ethyl acetate (75 mL) and water (25 mL) were added. The organic phase was washed with water (4 x 25 mL), dried (MgSO_4) and evaporated under reduced pressure. The residue was dissolved in ethanol (100 mL), palladium on carbon (10%, 100 mg) was added and the mixture was shaken under hydrogen (50 p.s.i.) for 4.5 h. Further palladium on carbon (10%, 100 mg) was added and the mixture was shaken under hydrogen (50 p.s.i.) for 1.5 h. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to give 3-amino-2,3-dihydro-1-(2-dimethylaminoethyl)-5-phenyl-1H-1,4-benzodiazepin-2-one (180 mg, 17%).

30 δ_{H} (CDCl_3) 7.75-7.17 (9H, m), 4.45 (1H, s), 4.40 (1H, m), 3.82 (1H, m), 2.47 (4H, m), and 2.08 (6H, s).

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Step E:

N-[2,3-Dihydro-1-(2-dimethylaminoethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide

15 Triethylamine was added to a mixture of 3-amino-2,3-dihydro-1-(2-dimethylaminoethyl)-5-phenyl-1H-1,4-benzodiazepin-2-one (180 mg, 0.6 mmol), 3-(2,4-dichlorophenyl)propanoic acid (131 mg, 0.6 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (115 mg, 0.6 mmol) and 1-hydroxybenzotriazole (81 mg, 0.6 mmol) in DMF (15 mL) until the pH was 9.0. The mixture was

20 stirred at room temperature for 72 h. The solvent was evaporated under reduced pressure and ethyl acetate was added. The mixture was washed with water, saturated aqueous sodium hydrogen carbonate and water, dried (MgSO₄) and evaporated under reduced pressure. The residue was triturated with acetone and recrystallized from i-

25 PrOH/MeOH to give N-[2,3-dihydro-1-(2-dimethylaminoethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide as a solid, m.p. 199-201°C.

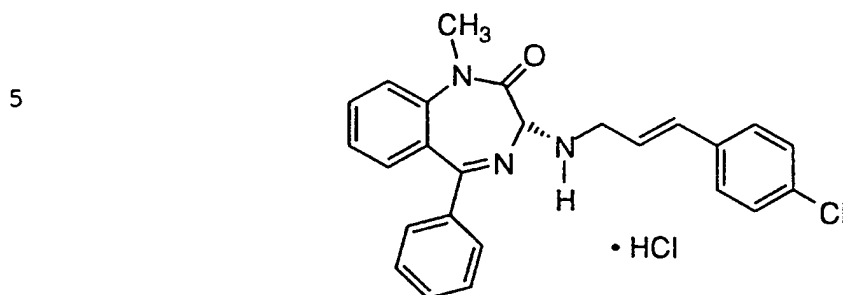
30 δ H (CDCl₃) 7.60-7.15 (13H, m), 5.50 (1H, d, J 8.0 Hz), 4.40 (1H, m), 3.80 (1H, m), 3.10 (2H, t, J 7.5 Hz), 2.70 (2H, t, J 7.5 Hz), 2.40 (2H, m), and 2.05 (6H, s).

Anal. Calcd. for C₂₈H₂₈Cl₂N₄O₂:

C, 64.25; H, 5.39; N, 10.70.

Found: C, 64.23; H, 5.40; N, 10.61%.

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EXAMPLE 61

(+)-3(R)-{N-[3-(4-chlorophenyl)prop-1-en-3-yl]amino}-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one hydrochloride

A mixture of 3(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (*J. Org. Chem.* 1987, 52, 3232-3239) (265 mg, 1 mmol), *E*-1-chloro-4-(3-chloro-1-propenyl)benzene (281 mg, 1.5 mmol), potassium carbonate (276 mg, 2 mmol) and potassium iodide (25 mg, 0.15 mmol) in acetonitrile (2 mL) was heated under reflux for 4 h. The mixture was cooled and poured into ethyl acetate (10 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic fractions were washed with brine, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/Hexane (65:35 increasing to 100:0). The first compound to elute was suspended in ethanol (1 mL) and ethanolic HCl (6 M, 0.11 mL) was added. The mixture was stirred, then the solvent was evaporated under reduced pressure. The residue was triturated with ether and the solid was collected and dried in vacuo to give (+)-3(R)-{N,N-bis[1-(4-chlorophenyl)propen-3-yl]amino}-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one hydrochloride (235 mg, 39%) as a tan solid, m.p. 138-145°C, [α]_D +9.2° (c=0.500, MeOH).
 δ _H (d₆-DMSO) 11.2 (1H, br s), 7.77-7.31 (17H, m), 6.85 (2H, br m), 6.54 (2H, m), 5.20 (1H, br s), 4.60-4.00 (4H, m), and 3.46 (3H, s).
Anal. Calcd. for C₃₄H₂₉Cl₂N₃O.HCl.0.10EtOH:

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C, 67.60; H, 5.08; N, 6.92.

Found: C, 67.60; H, 5.03; N, 7.03%.

The second compound to elute was suspended in ethanol (0.5 mL) and ethanolic HCl (6 M, 0.035 mL) was added. The mixture was stirred, then the solvent was evaporated under reduced pressure. The residue was triturated with ether and the solid was collected and dried in vacuo to give (+)-3(R)-{N-[3-(4-chlorophenyl)propen-3-yl]amino}-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one hydro-chloride (56 mg, 12%) as a yellow solid, m.p. 156-162°C, $[\alpha]_D^{+35}$ (c=0.100, MeOH).

δ_H (d₆-DMSO) 10.3 (1H, br s), 10.0 (1H, br s), 7.79-7.34 (13H, m), 6.78 (1H, d, J 15.9 Hz), 6.40 (1H, dt, J_d 15.9, J_t 9.0 Hz), 5.13 (1H, s), 4.00 (2H, m), and 3.46 (3H, s).

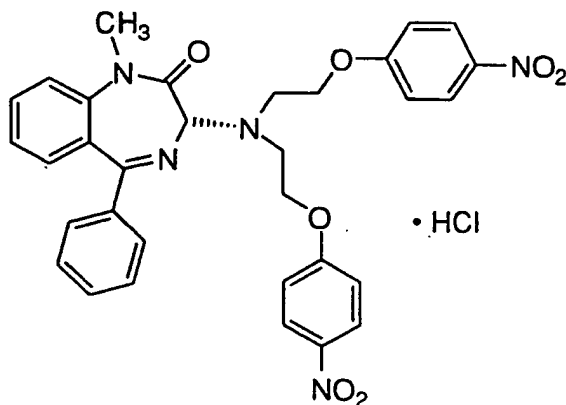
Anal. Calcd. for C₂₅H₂₂ClN₃O.HCl.0.10EtOH.0.40H₂O:

C, 65.20; H, 5.30; N, 9.05.

Found: C, 65.14; H, 5.09; N, 9.33%.

Employing the procedure substantially as described above, but substituting 1-(2-bromoethoxy)-4-nitrobenzene or 4-chlorobenzene-propanol methanesulfonate for the E-1-chloro-4-(3-chloro-1-propenyl)-benzene, the following compounds were prepared:

EXAMPLE 62



- 98 -

(+)-3(S)-{N,N-Bis[2-(4-nitrophenoxy)ethyl]amino}-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one hydrochloride
m.p. 126-145°C, $[\alpha]_D +5.0^\circ(0.100, \text{CHCl}_3)$.

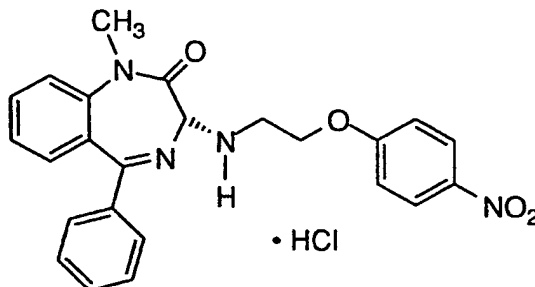
δ_H (d₆-DMSO) 8.20 (4H, d, J 9.2 Hz), 7.75-7.36 (9H, m), 7.08 (4H, d, J 9.2 Hz), 4.90 (1H, br s), 4.50 (4H, br s), 4.30-3.60 (5H, br m), and 3.34 (3H, s).

Anal. Calcd. for C₃₂H₂₉N₅O₇.HCl.0.15EtOH:

C, 60.71; H, 4.87; N, 10.96.

Found: C, 60.70; H, 4.87; N, 10.70%.

EXAMPLE 63



(+)-3(R)-{N-[3-(4-Nitrophenoxy)ethyl]amino}-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one hydrochloride
m.p. 154-160°C, $[\alpha]_D +84.6^\circ(0.500, \text{MeOH})$.

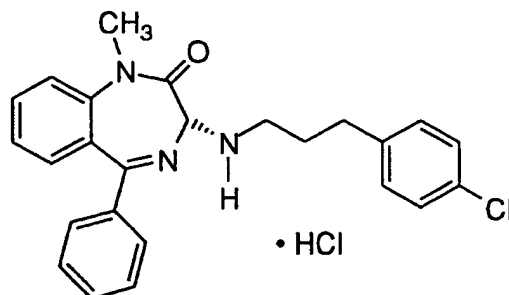
δ_H (d₆-DMSO) 10.2 (1H, br s), 8.25 (2H, d, J 9.0 Hz), 7.83-7.41 (9H, m), 7.09 (2H, d, J 9.0 Hz), 5.21 (1H, s), 4.57 (2H, m), 3.70 (2H, m), 3.47 (3H, s), and 3.40 (1H, m).

Anal. Calcd. for C₂₄H₂₂N₄O₄.HCl.0.15EtOH.0.20H₂O:

C, 61.13; H, 5.13; N, 11.74.

Found: C, 61.12; H, 4.92; N, 11.64%.

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EXAMPLE 64

(+)-3(R)-{N-[3-(4-Chlorophenyl)prop-1-yl]amino}-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one hydrochloride

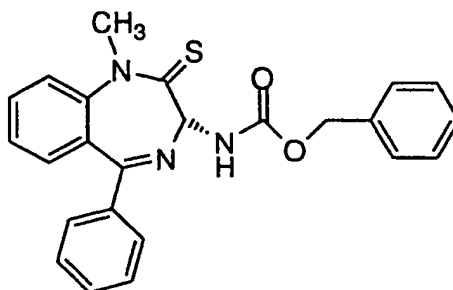
m.p. 167-168°C, $[\alpha]_D^{20} +20.8^\circ$ (c=0.500, MeOH).

δ_H (d₆-DMSO) 9.9 (2H, br m), 7.78-7.26 (13H, m), 5.08 (1H, s), 3.45 (3H, s), 3.20 (1H, m), 3.00 (1H, m), 2.70 (2H, t, J 7.4 Hz), and 2.05 (2H, m).

Anal. Calcd. for C₂₅H₂₄ClN₃O.HCl:

C, 66.08; H, 5.55; N, 9.25.

Found: C, 65.81; H, 5.49; N, 9.30%.

EXAMPLE 65

(+)-Phenylmethyl N-[(3R)-2,3-dihydro-1-methyl-5-phenyl-2-thioxo-1H-1,4-benzodiazepin-3-yl]carbamate

A mixture of (+)-phenylmethyl N-[(3R)-2,3-dihydro-1-methyl-5-phenyl-2-oxo-1H-1,4-benzodiazepin-3-yl]carbamate (4.0 g, 10

- 100 -

mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (4.5 g, 11 mmol) in toluene (100 mL) was heated under reflux for 75 min. The mixture was cooled and the volume was reduced to 30 mL by evaporation under reduced pressure. The residue was purified
5 by flash column chromatography on silica gel, eluting with EtOAc/Hexane (75:25) to give (+)-phenylmethyl N-[(3R)-2,3-dihydro-1-methyl-5-phenyl-2-thioxo-1H-1,4-benzodiazepin-3-yl]carbamate as a solid, m.p. 128-131°C, $[\alpha]_D^{25} +22.5^\circ$ (c=0.656, CHCl₃).
10 δ_H (CDCl₃) 7.65-7.26 (15H, m), 5.50 (1H, d, J 8.8 Hz), 5.14 (2H, s), and 3.86 (3H, s).

Anal. Calcd. for C₂₄H₂₁N₃O₂S.0.25H₂O:

C, 68.63; H, 5.16; N, 10.01.

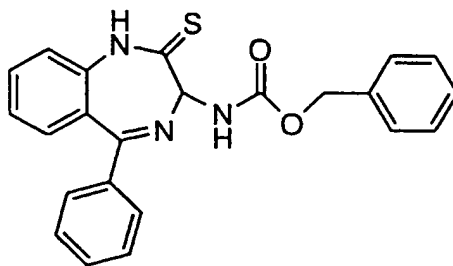
Found: C, 68.28; H, 5.21; N, 10.06%.

15 Employing the procedure substantially as described above, but substituting phenylmethyl N-[2,3-dihydro-5-phenyl-2-oxo-1H-1,4-benzodiazepin-3-yl]carbamate for the (+)-phenylmethyl N-[(3R)-2,3-dihydro-1-methyl-5-phenyl-2-oxo-1H-1,4-benzodiazepin-3-yl]carbamate, the following compound was prepared:

20

EXAMPLE 66

25

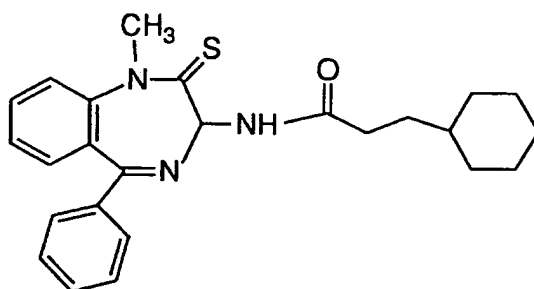


30

Phenylmethyl N-[2,3-dihydro-5-phenyl-2-thioxo-1H-1,4-benzodiazepin-3-yl]carbamate

δ_H (d₆-DMSO) 10.85 (1H, s), 8.42 (1H, d, J 8.6 Hz), 7.65-7.10 (14H, m), 5.10 (2H, s), and 5.05 (1H, d, J 8.6 Hz).

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EXAMPLE 67

3-Cyclohexyl-N-(2,3-dihydro-1-methyl-5-phenyl-2-thioxo-1H-1,4-benzodiazepin-3-yl)propanamide

Hydrogen bromide was bubbled at room temperature through a solution of (+)-phenylmethyl N-[(3R)-2,3-dihydro-1-methyl-5-phenyl-2-thioxo-1H-1,4-benzodiazepin-3-yl]carbamate (0.9 g, 2.1 mmol), acetic acid (5 mL) and dichloromethane (5 mL). After 2 h., the solvent was evaporated under reduced pressure, ether was added and the solid was collected and dried in vacuo. A sample (0.58 g, 1.8 mmol) was suspended in THF (10 mL), triethylamine (0.24 mL, 0.18 g, 1.8 mmol) was added and the mixture was stirred at room temperature for 3 h. In a separate flask, oxalyl chloride (0.20 mL, 0.29 g, 2.3 mmol) was added to a solution of cyclohexanepropionic acid (0.33 mL, 0.30 g, 1.9 mmol) and DMF (1 drop) in THF (10 mL) and the mixture was stirred at room temperature for 3 h. The two mixtures were combined, triethylamine (0.32 mL, 0.23 g, 2.3 mmol) was added and the mixture was stirred at room temperature for 2.5 h. The solvent was evaporated under reduced pressure, water was added and the mixture was extracted with ethyl acetate. The combined organic fractions were washed with water, saturated aqueous sodium hydrogen carbonate, water (2 x) and brine, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH₂Cl₂/MeOH (99.5:0.5) and the residue was recrystallized from EtOAc/Hexane to give 3-cyclohexyl-N-(2,3-

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dihydro-1-methyl-5-phenyl-2-thioxo-1H-1,4-benzodiazepin-3-yl)propanamide as a solid, m.p. 219-221°C.

δ H (CDCl₃) 7.95 (1H, br d, J 8.6 Hz), 7.65-7.30 (9H, m), 5.72 (1H, d, J 8.6 Hz), 3.87 (3H, s), 2.41 (2H, t, J 7.6 Hz), and 1.80-0.85 (13H, m).

5 Anal. Calcd. for C₂₅H₂₉N₃OS.0.25H₂O:

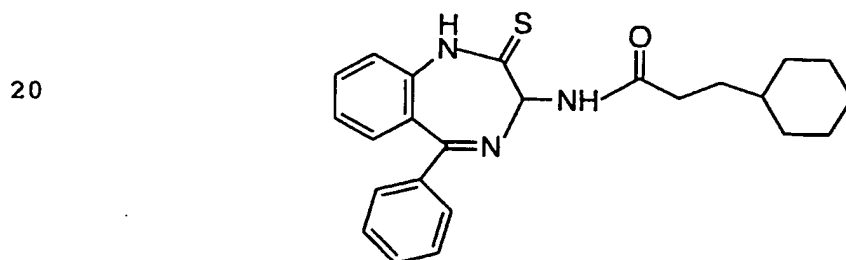
C, 70.81; H, 7.01; N, 9.91.

Found: C, 70.80; H, 6.91; N, 9.95%.

Employing the procedure substantially as described above,
10 but substituting phenylmethyl N-[2,3-dihydro-5-phenyl-2-thioxo-1H-1,4-benzodiazepin-3-yl]carbamate for the (+)-phenylmethyl N-[(3R)-2,3-dihydro-1-methyl-5-phenyl-2-thioxo-1H-1,4-benzodiazepin-3-yl]carbamate and an appropriate acid for the cyclohexanepropionic acid, the following compounds were prepared:

15

EXAMPLE 68



25 3-Cyclohexyl-N-(2,3-dihydro-5-phenyl-2-thioxo-1H-1,4-benzodiazepin-3-yl)propanamide

m.p. 113-119°C.

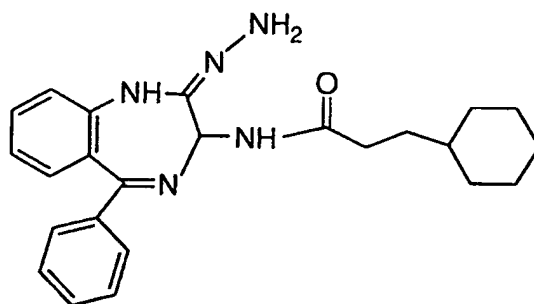
δ H (CDCl₃) 9.8 (1H, br s), 7.75-7.25 (10H, m), 5.75 (1H, d, J 8.1 Hz), 2.41 (2H, m), and 1.80-0.85 (13H, m).

30 Anal. Calcd. for C₂₄H₂₇N₃OS.0.8CH₂Cl₂:

C, 62.91; H, 6.09; N, 8.87.

Found: C, 62.88; H, 5.70; N, 9.12%.

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EXAMPLE 693-Cyclohexyl-N-(2,3-dihydro-2-hydrazono-5-phenyl-1H-1,4-benzodiazepin-3-yl)propanamide

Hydrazine (53 μ L, 56 mg, 1.8 mmol) was added to a solution of 3-cyclohexyl-N-(2,3-dihydro-1-methyl-5-phenyl-2-thioxo-1H-1,4-benzodiazepin-3-yl)propanamide (120 mg, 0.25 mmol) in methanol (3 mL). The mixture was stirred at room temperature for 3 h. and the solvent was evaporated under reduced pressure. Ethyl acetate was added and the mixture was washed with water and brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (99.5:0.5 increasing to 98:2) to give 3-cyclohexyl-N-(2,3-dihydro-2-hydrazono-5-phenyl-1H-1,4-benzodiazepin-3-yl)propanamide as a foam.

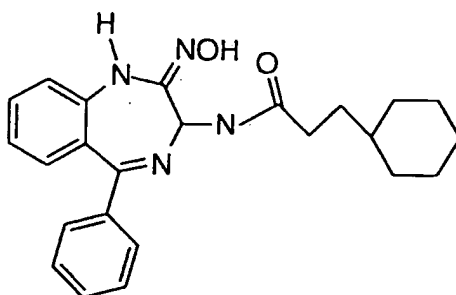
δ_{H} (CDCl_3) 7.55-7.00 (11H, m), 5.75 (1H, d, J 7.6 Hz), 3.50 (2H, br s), 2.37 (2H, t, J 8.0 Hz), and 1.80-0.85 (13H, m).

Anal. Calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_5\text{O} \cdot 0.8\text{CH}_3\text{OH} \cdot 0.15\text{CH}_2\text{Cl}_2$:

C, 67.82; H, 7.41; N, 15.85.

Found: C, 67.79; H, 7.46; N, 16.05%.

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EXAMPLE 70

(E)- and (Z)-3-Cyclohexyl-N-(2,3-dihydro-2-hydroxyimino-5-phenyl-1H-1,4-benzodiazepin-3-yl)propanamide

A mixture of 3-cyclohexyl-N-(2,3-dihydro-1-methyl-5-phenyl-2-thioxo-1H-1,4-benzodiazepin-3-yl)propanamide (740 mg, 1.83 mmol), hydroxylamine hydrochloride (140 mg, 2 mmol) and triethylamine (280 μ L, 203 mg, 2 mmol) in methanol (15 mL)/THF (15 mL) was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with CH₂Cl₂/MeOH (98:2). The residue recrystallized from ethyl acetate. The first isomer to crystallize was recrystallized from ethyl acetate to give (E)-3-cyclohexyl-N-(2,3-dihydro-2-hydroxyimino-5-phenyl-1H-1,4-benzodiazepin-3-yl)propanamide as a solid, m.p. 196°C. δ _H (d₆-DMSO) 12.20 (1H, s), 9.00 (1H, d, J 8.0 Hz), 7.70-7.30 (10H, m), 5.45 (1H, d, J 8.0 Hz), 2.30 (2H, m), and 1.80-0.75 (13H, m).

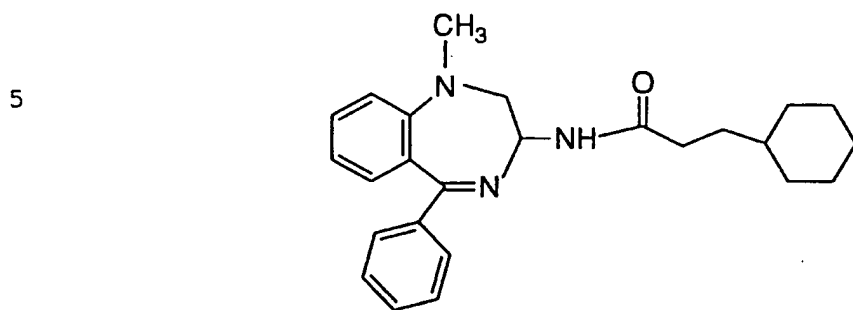
The second isomer to crystallize was recrystallized from methanol to give (Z)-3-cyclohexyl-N-(2,3-dihydro-2-hydroxyimino-5-phenyl-1H-1,4-benzodiazepin-3-yl)propanamide as a solid, m.p. 219°C. δ _H (d₆-DMSO) 9.95 (1H, s), 8.95 (1H, s), 8.75 (1H, d, J 8.0 Hz), 7.50-7.00 (9H, m), 5.70 (1H, d, J 8.0 Hz), 2.25 (2H, m), and 1.75-0.75 (13H, m).

Anal. Calcd. for C₂₄H₂₈N₄O₂:

C, 71.26; H, 6.98; N, 13.85.

Found: C, 70.89; H, 6.99; N, 13.55%.

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EXAMPLE 713-Cyclohexyl-N-(2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-3-yl) propanamide

Freshly prepared Raney nickel (400 mg) was added to a solution of 3-cyclohexyl-N-(2,3-dihydro-1-methyl-5-phenyl-2-thioxo-1H-1,4-benzodiazepin-3-yl)propanamide (200 mg, 0.5 mmol) in ethanol (20 mL) and the mixture was stirred at room temperature for 2 h. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH₂Cl₂/MeOH (99.75:0.25) to give 3-cyclohexyl-N-(2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-3-yl) propanamide as a foam.

δ H (CDCl₃) 7.60-6.80 (9H, m), 6.37 (1H, br d, J 6.6 Hz), 5.53 (1H, m), 3.60 (2H, m), 2.77 (3H, s), 2.21 (2H, t, J 8.0 Hz), and 1.85-0.80 (13H, m).

Anal. Calcd. for C₂₅H₃₁N₃O.0.2CH₂Cl₂:

C, 74.45; H, 7.79; N, 10.34.

Found: C, 74.68; H, 7.87; N, 10.23%.

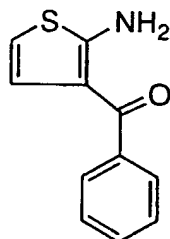
EXAMPLE 72

1-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-thieno-[2,3-e]-1,4-diazepin-3-yl)-3-(3-methyl-phenyl)urea

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Step A:

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(2-Amino-3-thienyl)phenylmethanone

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Triethylamine (6.8 mL, 4.94 g, 49 mmol) was added to a heated (33°C) mixture of β -oxobenzene-propanenitrile (18.6 g, 128 mmol) and 1,2-dithiane-2,5-diol (9.8 g, 64 mmol) in ethanol (120 mL) and the mixture was stirred at 50°C for 18 h. The mixture was cooled and the solvent was evaporated under reduced pressure.

15

Dichloromethane was added, the mixture was washed with aqueous hydrochloric acid (0.5M), aqueous sodium hydroxide (1M) and brine, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure.

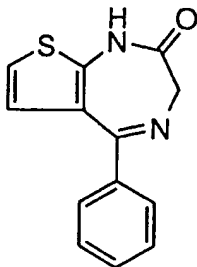
The residue was recrystallized from acetonitrile (150 mL) to give (2-amino-3-thienyl)-phenylmethanone as an orange solid (5.7 g, 44%).

20

δ H (CDCl₃) 7.70-7.35 (5H, m), 6.95 (2H, br s), 6.90 (1H, d, J 6.3 Hz), and 6.15 (1H, d, J 6.3 Hz).

Step B:

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2,3-Dihydro-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-2-one

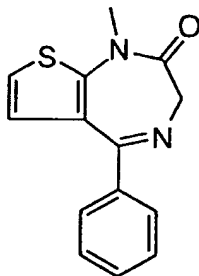
A solution of 1,3-dihydro-1,3-dioxo-2H-isoindole-2-acetyl chloride (8.6 g, 38 mmol) in dichloromethane (20 mL) was added

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slowly to a cooled (0°C) mixture of (2-amino-3-thienyl)phenyl-methanone (6.8 g, 33 mmol), pyridine (6.34 mL, 6.20 g, 78 mmol) and 4-dimethylamino-pyridine (0.79 g, 6.5 mmol) in dichloromethane (130 mL). The mixture was stirred at 0°C for 30 min., diluted with
5 dichloromethane (80 mL) and washed with aqueous hydrochloric acid (1M), saturated aqueous sodium hydrogen carbonate and brine. The mixture was dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was triturated with ethanol and the solid was collected and dried in vacuo to give N-(3-benzoylthien-2-yl)-1,3-
10 dihydro-1,3-dioxo-2H-isoindole-2-acetamide as a solid (9.8 g, 76%).

A mixture of N-(3-benzoylthien-2-yl)-1,3-dihydro-1,3-dioxo-2H-isoindole-2-acetamide (10.9 g, 28 mmol) and hydrazine (1.9 mL, 1.94 g, 60 mmol) in THF (500 mL) was heated under reflux for 4 h. The mixture was cooled, filtered and the solvent was evaporated
15 under reduced pressure. Saturated aqueous sodium hydrogen carbonate was added and the mixture was extracted with ethyl acetate. The combined organic fractions were washed with brine, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. Acetic acid (300 mL) was added and the mixture was heated under reflux for 15
20 min. The mixture was cooled and the solvent was evaporated under reduced pressure. Saturated aqueous sodium hydrogen carbonate was added and the mixture was extracted with ethyl acetate. The combined organic fractions were washed with brine, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure to give 2,3-dihydro-5-
25 phenyl-1H-thieno[2,3-e]-1,4-diazepin-2-one as a foam (3.5 g, 52%).
δH (CDCl₃) 9.75 (1H, br s), 7.90-7.30 (5H, m), 6.87 (1H, d, J 6.0 Hz), 6.82 (1H, d, J 6.0 Hz), and 4.45 (2H, s).

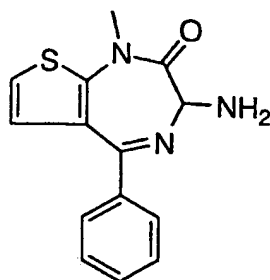
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Step C:

10 2,3-Dihydro-1-methyl-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-2-one

Sodium hydride (60% dispersion in mineral oil, 757 mg, 11.3 mmol) was added to a cooled (0°C) solution of 2,3-dihydro-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-2-one (2.61 g, 10.8 mmol) in DMF (7 mL). Further DMF (10 mL) was added and the mixture was stirred for 30 min. A solution of iodomethane (0.67 mL, 1.53 g, 10.8 mmol) in ether (20 mL) was added and the mixture was stirred for 1 h. The mixture was poured into water and the mixture was extracted with ethyl acetate. The combined organic fractions were washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH₂Cl₂/MeOH (95:5) to give 2,3-dihydro-1-methyl-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-2-one (1.5 g, 54%).

25 δ H (CDCl₃) 7.67-7.35 (5H, m), 7.00 (1H, d, J 6.0 Hz), 6.85 (1H, d, J 6.0 Hz), 4.45 (2H, br s), and 3.50 (3H, s).

Step D:

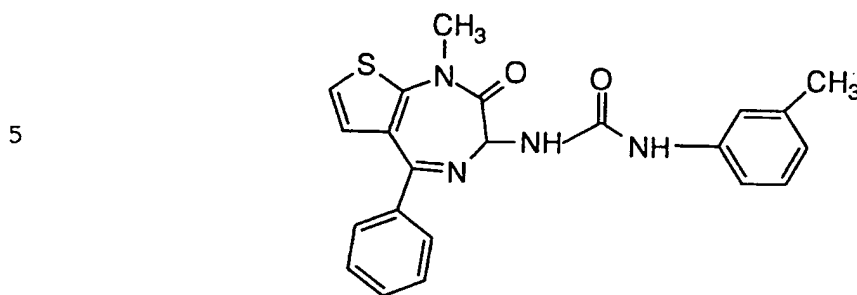
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3-Amino-2,3-dihydro-1-methyl-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-2-one

2,3-Dihydro-1-methyl-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-2-one (1.5 g, 5.8 mmol) was dissolved in toluene (30 mL).
5 The mixture was cooled to -10°C and potassium t-butoxide (1.7 g, 15.1 mmol) was added. The mixture was stirred at -10°C for 15 min., then isoamyl nitrite (1.0 mL, 0.87 g, 7.4 mmol) was added. The mixture was stirred at -10°C for 1 h. then allowed to warm to room temperature and poured into water (50 mL) and acetic acid (3 mL). The mixture
10 was extracted with ethyl acetate and the combined organic fractions were washed with brine, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/Hexane to give 2,3-dihydro-1-methyl-3-hydroxyimino-5-phenyl-1H-thieno[2,3-e]-
15 1,4-diazepin-2-one (0.80 g, 48%).

2,3-Dihydro-1-methyl-3-hydroxyimino-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-2-one (0.80 g, 2.8 mmol) was dissolved in ethanol (40 mL) and Raney nickel (2 g) was added. The mixture was shaken under hydrogen (50 p.s.i.) for 5 days, adding further Raney
20 nickel (10 g) in portions. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH₂Cl₂/MeOH to give 3-amino-2,3-dihydro-1-methyl-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-2-one (248 mg, 33%).
25 δ H (CDCl₃) 7.50-7.30 (5H, m), 7.05 (1H, d, J 6.0 Hz), 6.85 (1H, d, J 6.0 Hz), 4.57 (1H, s), 3.55 (3H, s), and 1.70 (2H, br s).

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Step E:

10 1-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-3-yl)-3-(3-methylphenyl)urea

3-Methylphenylisocyanate (60 μ L, 62 mg, 0.46 mmol) was added to a solution of 3-amino-2,3-dihydro-1-methyl-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-2-one (124 mg, 0.46 mmol) in tetrahydrofuran (5 mL). The mixture was stirred at room temperature for 2 h. and the solvent was evaporated under reduced pressure. The residue was crystallized from EtOAc (4 mL) to give 1-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-3-yl)-3-(3-methylphenyl)urea as a solid (94 mg, 50%).

20 m.p. 128-130°C.

δ H (CDCl₃) 8.70 (1H, s), 7.65-6.75 (12H, m), 5.55 (1H, d, J 9.0 Hz), 3.55 (3H, s), and 2.30 (3H, s).

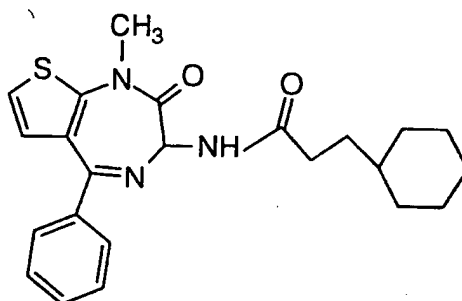
Anal. Calcd. for C₂₂H₂₀N₄O₂S.0.25H₂O:

C, 64.62; H, 4.99; N, 13.70.

25 Found: C, 64.68; H, 4.96; N, 13.70%.

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EXAMPLE 733-Cyclohexyl-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-3-yl)propanamide

Triethylamine (75 μ L, 54 mg, 0.54 mmol) was added to a mixture of 3-amino-2,3-dihydro-1-methyl-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-2-one (82 mg, 0.3 mmol), cyclohexanepropanoic acid (52 μ L, 47 mg, 0.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (58 mg, 0.3 mmol) and 1-hydroxybenzotriazole (42 mg, 0.3 mmol) in DMF (1.5 mL). The mixture was stirred at room temperature for 18 h. and ethyl acetate (60 mL) was added. The mixture was washed with aqueous citric acid (10%), saturated aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/Hexane to give 3-cyclohexyl-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-thieno[2,3-e]-1,4-diazepin-3-yl)propanamide as a solid (56 mg, 46%). m.p. 189-190°C.

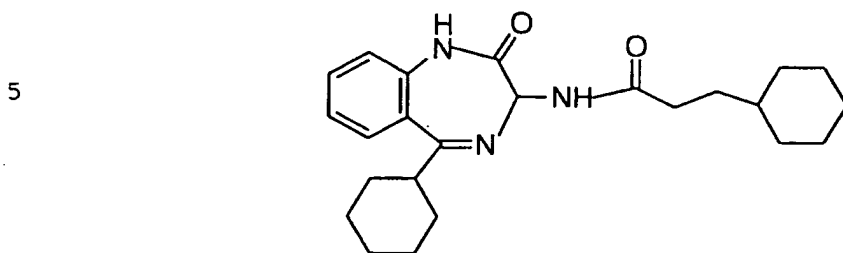
δ_{H} (CDCl_3) 7.65-6.85 (8H, m), 5.65 (1H, d, J 8.0 Hz), 3.55 (3H, s), 2.40 (2H, t, J 7.0 Hz), and 1.80-0.85 (13H, m).

Anal. Calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_2\text{S} \cdot 0.5\text{H}_2\text{O}$:

C, 66.00; H, 6.74; N, 10.04.

Found: C, 66.25; H, 6.76; N, 9.83%.

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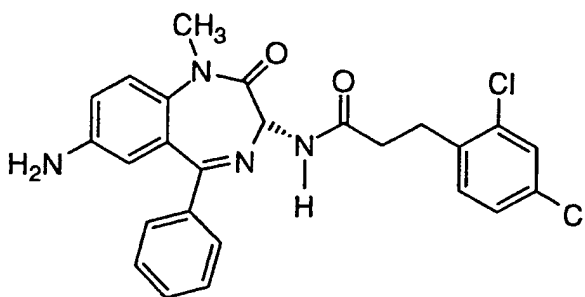
EXAMPLE 74

10 3-Cyclohexyl-N-(5-cyclohexyl-2,3-dihydro-2-oxo-1H-1,4-benzodiazepin-3-yl) propanamide

Phenylmethyl N-[5-cyclohexyl-2,3-dihydro-2-oxo-1H-1,4-benzodiazepin-3-yl]carbamate (150 mg, 0.38 mmol) was dissolved in hydrogen bromide in acetic acid (30%, 0.5 mL). After 2 h., ether was added and the solid was collected and dried in vacuo. THF (3 mL) and triethylamine (0.45 μ L, 33 mg, 0.32 mmol) were added and the mixture was stirred at room temperature for 3 h. In a separate flask, oxalyl chloride (38 μ L, 56 mg, 0.44 mmol) was added to a solution of cyclohexanepropionic acid (61 μ L, 56 mg, 0.36 mmol) and DMF (1 drop) in THF (2 mL) and the mixture was stirred at room temperature for 3 h. The two mixtures were combined, triethylamine (61 μ L, 44 mg, 0.44 mmol) was added and the mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and ethyl acetate was added. The mixture was washed with water (2 x), saturated aqueous sodium hydrogen carbonate, water and brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was recrystallized from i-PrOH to give 3-cyclohexyl-N-(5-cyclohexyl-2,3-dihydro-2-oxo-1H-1,4-benzodiazepin-3-yl)propanamide as a solid, m.p. 133-138°C.

30 δ H (CDCl_3) 7.85 (1H, br s), 7.62-6.95 (5H, m), 5.40 (1H, d, J 8.7 Hz), 2.77 (1H, m), 2.34 (2H, m), and 2.05-0.75 (23H, m).
Anal. Calcd. for $\text{C}_{24}\text{H}_{33}\text{N}_3\text{O}_2 \cdot 0.7\text{C}_3\text{H}_7\text{OH}$:
C, 71.64; H, 8.89; N, 9.60.
Found: C, 71.28; H, 8.70; N, 9.82%.

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EXAMPLE 75

(+)-N-[(3R)-7-Amino-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide

Step A:

To a mixture of 3(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (*J. Org. Chem.* 1987, 52, 3232-3239) (3.98 g, 15.0 mmol) in concentrated sulfuric acid (15 mL) cooled in an ice-bath was added dropwise a solution of potassium nitrate (2.12 g, 21.0 mmol) in concentrated sulfuric acid (6 mL). The mixture was stirred with cooling for 2 h., then stirred at ambient temperature for 1.5 h. Ice (80 g) was added and the mixture was basified with concentrated ammonium hydroxide to pH 9. The resulting mixture was extracted with ethyl acetate (3 x 220 mL). The combined organic fractions were washed with brine, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with chloroform/methanol (97:3). The material which eluted was further purified by flash column chromatography on silica gel, eluting with ethyl acetate/methanol (95:5). The material which eluted was stirred under *n*-butyl chloride (30 mL) and the solvent was evaporated under reduced pressure to give an inseparable mixture of 3(R)-amino-1,3-dihydro-1-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one and 3(R)-amino-1,3-dihydro-1-methyl-7-nitro-5-(2-nitrophenyl)-2H-1,4-benzodiazepin-2-one (3.81 g) in a 3:1 ratio as a yellow solid.

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δ H (CDCl₃) (mononitro compound) 8.43 (1H, dd, J 9, 3 Hz), 8.23 (1H, d, J 3 Hz), 7.59 (2H, m), 7.52 (2H, m), 7.44 (2H, m), 4.47 (1H, s), 3.53 (3H, s), and 2.42 (2H, br s); (dinitro compound) 8.49 (1H, dd, J 9, 3), 8.42 (1H, m), 8.18 (1H, d, J 3 Hz), 8.01 (1H, m), 7.67 (1H, t, J 6 Hz),
5 7.6-7.4 (2H, m), 4.52 (1H, s), 3.56 (3H, s), and 2.42 (2H, br s).

Step B:

A solution of 3-(2,4-dichlorophenyl)propionic acid (482 mg, 2.2 mmol), DMF (0.017 mL, 0.22 mmol), and thionyl chloride
10 (0.24 mL, 3.3 mmol) in chloroform (2.5 mL) was heated at reflux for 1 h. The solvent was evaporated under reduced pressure to give 3-(2,4-dichlorophenyl)propionyl chloride (520 mg, 100%). To a solution of mixed 3(R)-amino-1,3-dihydro-1-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one and 3(R)-amino-1,3-dihydro-1-methyl-7-nitro-5-
15 (2-nitrophenyl)-2H-1,4-benzodiazepin-2-one (3:1) (621 mg, 2 mmol) and triethylamine (0.305 mL, 2.2 mmol) in methylene chloride (10 mL), was added a solution of 3-(2,4-dichlorophenyl)propionyl chloride (520 mg, 2.2 mmol) in methylene chloride (1.5 mL). The mixture was stirred for 30 min., the solvent was partially evaporated under reduced
20 pressure, and the reaction mixture was purified by flash column chromatography on silica gel, eluting with methylene chloride/ether (90:10) to give a mixture of (+)-N-[(3R)-2,3-dihydro-1-methyl-7-nitro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)-propanamide and (+)-N-[(3R)-2,3-dihydro-1-methyl-7-nitro-2-oxo-5-
25 (2-nitrophenyl)-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)-propanamide (850 mg, 84%) in a 3:1 ratio as a solid white foam.
 δ H (CDCl₃) (mononitro compound) 8.45 (1H, dd, J 9, 3 Hz), 8.25 (1H, d J 3 Hz), 7.54 (3H, m), 7.45 (2H, m), 7.38 (1H, d, J 2 Hz), 7.26-7.18 (4H, m), 5.50 (1H, d, J 8 Hz), 3.52 (3H, s), 3.10 (2H, m), and 2.70 (2H, m); (dinitro compound) 8.51 (1H, dd, J 9, 3 Hz), 8.40 (1H, m), 8.21
30 (1H, d J 3 Hz), 7.98 (1H, m), 7.68 (1H, t, J 6 Hz), 7.60 (1H, m), 7.44 (1H, m), 7.26-7.15 (4H, m), 5.52 (1H, d, J 8 Hz), 3.55 (3H, s), 3.10 (2H, m), and 2.70 (2H, m).

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Step C:

To a solution of mixed N-[(3R)-2,3-dihydro-1-methyl-7-nitro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide and (+)-N-[(3R)-2,3-dihydro-1-methyl-7-nitro-2-oxo-5-(2-nitrophenyl)-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide (3:1) (770 mg, 1.5 mmol) in acetic acid (6 mL) was added dropwise in portions over 1.5 h. a solution of 15% titanium (III) chloride in 20-30% hydrochloric acid (7.8 mL, 9.0 mmol). The resulting solution was stirred 30 min., basified with 20% sodium hydroxide solution (pH 9), diluted with water (80 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic fractions were washed with brine, dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexane (75:25 increasing to 100:0). The first compound to elute was crystallized from ethyl acetate to give (+)-N-[(3R)-7-amino-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide (413 mg, 57%) as a pale yellow solid, m.p. 179-180°C, [α]_D +60.2° (c= 0.500, CHCl₃).

δ H (CDCl₃) 7.60 (2H, d, J 7 Hz), 7.49-7.36 (5H, m) 7.24 (1H, d, J 9 Hz), 7.17 (2H, m), 6.99 (1H, dd, J 9, 3 Hz), 6.64 (1H, d, J 3 Hz), 5.54 (1H, d, J 8 Hz), 4.80-3.50 (2H, br s), 3.39 (3H, s), 3.09 (2H, t, J 8 Hz), and 2.68 (2H, dt, J_d 3, J_t 8 Hz).

Anal. Calcd. for C₂₅H₂₂Cl₂N₄O₂:

25 C, 62.38; H, 4.61; N, 11.64.

Found: C, 62.58; H, 4.68; N, 11.65%.

The second compound to elute was crystallized from ethyl acetate to give (+)-N-[(3R)-7-amino-2,3-dihydro-1-methyl-2-oxo-5-(2-aminophenyl)-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide (114 mg, 15%) as a pale yellow solid, m.p. 188-189°C, [α]_D +50.0° (c=0.100, MeOH).

δ H (CDCl₃) 7.36 (2H, m), 7.25 (1H, d, J 9 Hz), 7.15 (3H, m), 7.00 (1H,

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m), 6.88 (2H, m), 6.79 (1H, m), 6.60 (1H, bs), 5.52 (1H, d, J 8 Hz), 4.10-2.80 (4H br s), 3.40 (3H, m), 3.09 (2H, t, J 8 Hz), and 2.69 (2H, m).

Anal. Calcd. for $C_{25}H_{23}Cl_2N_5O_2 \cdot 0.05EtOAc$:

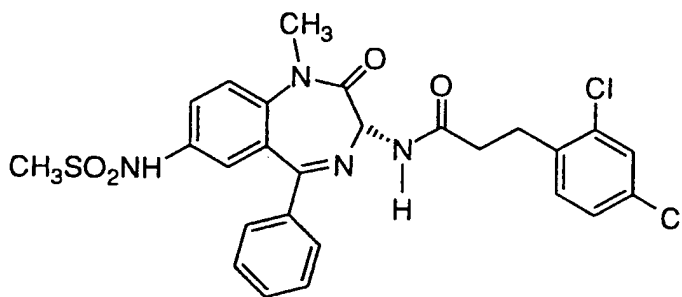
5 C, 60.43; H, 4.71; N, 13.99.

Found: C, 60.79; H, 4.74; N, 13.83%.

EXAMPLE 76

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(+)-N-[(3R)-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-7-methanesulfonamido-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide

Methanesulfonyl chloride (0.040 mL, 0.52 mmol) was added to a solution of (+)-N-[(3R)-7-amino-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide (193 mg, 0.40 mmol) and pyridine (0.065 mL, 0.80 mmol) in methylene chloride (1.6 mL). The resulting solution was stirred 2 h. The solution was diluted with ethyl acetate (12 mL), washed with 1N HCl, water, saturated sodium bicarbonate solution, water, and brine (3 mL each), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was dissolved in warm toluene, treated with charcoal, and filtered. The filtrate was diluted with hexane, the mixture was cooled, and the resulting precipitate was collected and dried in vacuo to give (+)-N-[(3R)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-7-methanesulfonamido-1H-1,4-benzodiazepin-3-yl]-3-

25
30

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(2,4-dichlorophenyl)propanamide (152 mg, 68%) as a white solid, m.p. 130-148°C, $[\alpha]_D +111.6^\circ$ ($c=0.500$, CHCl_3).

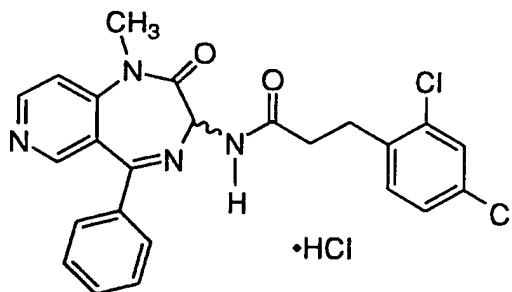
δ_H (CDCl_3) 7.55-7.32 (9H, m), 7.24 (2H, dd, J 10, 2 Hz), 7.17 (1H, dd, J 9, 2 Hz), 7.05 (1H, d, J 3 Hz), 5.49 (1H, d, J 8 Hz), 3.41 (3H, s), 3.08 (2H, t, J 8 Hz), 2.97 (3H, s), and 2.71 (2H, dt, J_d 3, J_t 8 Hz).

Anal. Calcd. for $\text{C}_{26}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_4\text{S}$:

C, 55.82; H, 4.32; N, 10.01.

Found: C, 56.12; H, 4.47; N, 9.89%.

EXAMPLE 77



N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepin-3-yl)-3-(2,4-dichlorophenyl)propanamide hydrochloride

Step A:

To a solution of 2,3-dihydro-1-methyl-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepine-2-one (*J. Med. Chem.*, 1965, 8, 722-724) (1.63 g, 6.5 mmol) in toluene (32 mL) under argon cooled to -20°C (ice/methanol bath) was added potassium t-butoxide (1.83 g, 16.3 mmol). The resulting purple suspension was stirred 15 min. at -20°C and isoamyl nitrite (1.05 mL, 7.8 mmol) was added. The mixture was stirred at -20°C for 30 min., then poured into a mixture of water (50 mL), acetic acid (3 mL), and ethyl acetate (65 mL). The mixture was stirred to dissolve all solids and the layers were separated. The aqueous layer was extracted with ethyl acetate (65 mL). The combined organic fractions were washed with saturated sodium bicarbonate solution and

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brine (20 mL each), dried (Na₂SO₄), and the solvent was evaporated under reduced pressure. The residue was triturated with cold toluene and the solid was collected and dried in vacuo to give 2,3-dihydro-3-hydroxyimino-1-methyl-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepine-2-one (1.22 g, 67%) as a yellow solid, m.p. 223-224°C.
5 δ H (CDCl₃) 8.92 (1H, bs), 8.73 (1H, d, J 7 Hz), 8.62 (1H, s), 7.80 (2H, dd, J 7, 1 Hz), 7.59 (1H, m), 7.48 (2H, m), 7.26 (1H, d, J 7 Hz), and 3.50 (3H, s).

10 Step B:

A mixture of 2,3-dihydro-3-hydroxyimino-1-methyl-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepine-2-one (1.77 g, 6.3 mmol) and freshly prepared Raney nickel (3.2 g) in 1:1 ethanol/methanol (190 mL) was shaken on a Parr hydrogenation apparatus under hydrogen (50 psi)
15 for 4 h. The mixture was filtered through filter aid and the filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with methanol/-chloroform/acetic acid (5:95:1 increasing to 10:90:1). The material which eluted was stirred under chloroform (30 mL) with potassium
20 carbonate (0.3 g) and water (0.2 mL) for 5 min. The mixture was dried (Na₂SO₄) and the solvent was evaporated under reduced pressure to give 3-amino-2,3-dihydro-1-methyl-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepine-2-one (276 mg, 16%), as a yellow solid, m.p. 109-123°C.
25 δ H (CDCl₃) 8.72 (1H, d, J 6 Hz), 8.58 (1H, s), 7.61 (2H, m), 7.51 (1H, m), 7.43 (2H, m), 7.26 (1H, m), 4.47 (1H, s), 3.50 (3H, s), and 2.1 (2H, bs).

High res. mass spectrum: Theoretical mass for C₁₅H₁₄N₄O (M+1): 267.124586. Measured mass (M+1): 267.123654.

30 Step C:

A solution of dicyclohexylcarbodiimide (87 mg, 0.42 mmol) in methylene chloride (0.17 mL) was added to a solution of 3-amino-2,3-dihydro-1-methyl-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepine-2-one (93 mg, 0.35 mmol) and 3-(2,4-dichlorophenyl)propionic acid

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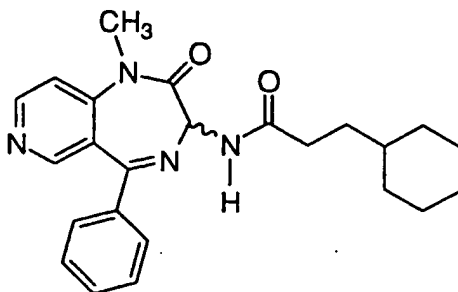
(83 mg, 0.38 mmol) in tetrahydrofuran (0.5 mL) under argon. The resulting mixture was stirred for 5 h., filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by preparative plate chromatography on silica gel eluting with methanol/chloroform/acetic acid (5:95:1). The purified material was stirred under chloroform (5 mL) with potassium carbonate (0.1 g) and water (2 drops) for 5 min. The mixture was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was suspended in ethanol (2 mL) and ethanolic HCl (6.8 M, 0.147 mL) was added. The mixture was stirred, the resulting precipitate was collected and dried in vacuo to give N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepin-3-yl)-3-(2,4-dichlorophenyl)propanamide hydrochloride (32 mg, 18%) as a white solid, m.p. 218-219°C. δ_{H} (d_6 -DMSO) 9.38 (1H, d, J 8 Hz), 8.86 (1H, bs), 8.59 (1H bs), 7.79 (1H, d, J 6 Hz), 7.56 (3H, m), 7.51 (2H, m), 7.39 (2H, m), 7.25 (1H, m), 7.16 (1H, m), 5.37 (1H, d, J 8 Hz), 3.44 (3H, s) 2.94 (2H, t, J 7 Hz), and 2.64 (2H, t, J 7 Hz).

Anal. Calcd. for $\text{C}_{24}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_2\cdot\text{HCl}$:

C, 57.22; H, 4.20; N, 11.12.

Found: C, 56.87; H, 4.18; N, 11.09%.

EXAMPLE 78



N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepin-3-yl)-3-(cyclohexyl)propanamide

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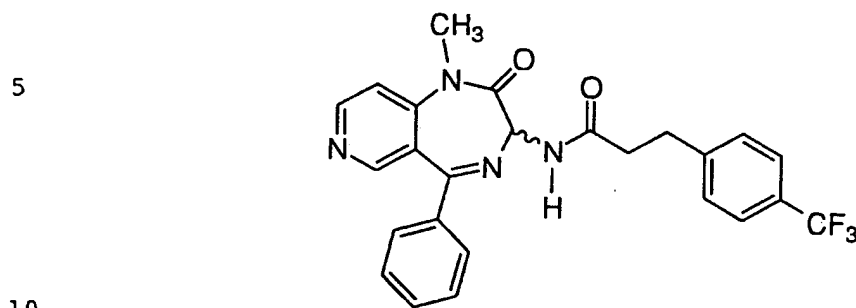
A solution of dicyclohexylcarbodiimide (87 mg, 0.42 mmol) in methylene chloride (0.17 mL) was added to a solution of 3-amino-2,3-dihydro-1-methyl-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepine-2-one (93 mg, 0.35 mmol) and cyclohexanepropionic acid (0.065 mL, 0.38 mmol) in tetrahydrofuran (0.5 mL) under argon. The resulting mixture was stirred for 5 h., filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by preparative plate chromatography on silica gel eluting with methanol/chloroform/acetic acid (5:95:1). The purified material was stirred under chloroform (5 mL) with potassium carbonate (0.1 g) and water (2 drops) for 5 min. The mixture was dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The residue was crystallized from toluene to give N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepin-3-yl)-3-(cyclohexyl)-propanamide (47 mg, 33%) as a white crystalline solid, m.p. 170-173°C.

δ H (CDCl₃) 8.75 (1H, d, J 6 Hz), 8.61 (1H, s), 7.58 (2H, m), 7.52 (1H, m), 7.45 (2H, m), 7.31 (1H, d, J 6 Hz), 7.21 (1H, d, J 8 Hz), 5.54 (1H, d, J 8 Hz), 3.51 (3H, s), 2.39 (2H, m), 1.73 (4H, m), 1.63 (3H, m), 1.85-1.12 (4H, m), and 0.94 (2H, m).

Anal. Calcd. for C₂₄H₂₈N₄O₂·0.10PhCH₃:
C, 71.70; H, 7.02; N, 13.54.
Found: C, 71.78; H, 7.01; N, 13.57%.

Employing the procedure substantially as described above, but substituting 3-(4-trifluoromethylphenyl)-propionic acid for the cyclohexanepropionic acid, the following compound was prepared:

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EXAMPLE 79

N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-pyrido[4,3-e]-1,4-diazepin-3-yl)-3-(4-trifluoromethylphenyl)propanamide

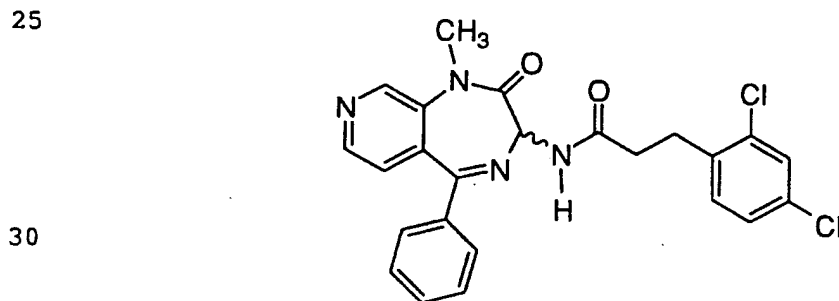
m.p. 191-192°C.

15 δ H (CDCl₃) 8.76 (1H, d, J 6 Hz), 8.61 (1H, s), 7.56 (4H, m), 7.52 (1H, m), 7.42 (2H, d, J 7 Hz), 7.38 (2H, m), 7.30 (1H, d, J 6 Hz), 7.22 (1H, d, J 8 Hz), 5.51 (1H, d, J 8 Hz), 3.50 (3H, s), 3.09 (2H, t, J 8 Hz), and 2.73 (2H, t, J 8 Hz).

Anal. Calcd. for C₂₅H₂₁F₃N₄O₂·0.20PhCH₃:

20 C, 65.39; H, 4.70; N, 11.56.

Found: C, 65.69; H, 4.64; N, 11.95%.

EXAMPLE 80

N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-pyrido[3,4-e]-1,4-diazepin-3-yl)-3-(2,4-dichlorophenyl)propanamide

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Step A:

To a solution of 2,3-dihydro-1-methyl-5-phenyl-1H-pyrido[3,4-e]-1,4-diazepine-2-one (Can. J. Chem. 1987, 65, 1158-1161) (1.43 g, 5.7mmol) in toluene (28 mL) under argon cooled to -20°C (ice/methanol bath) was added potassium t-butoxide (1.59 g, 14.2 mmol). The resulting purple suspension was stirred 15 min. at -20 °C and isoamyl nitrite (0.92 mL, 6.8 mmol) was added. The mixture was stirred at -20°C for 30 min., then poured into a mixture of water (25 mL), acetic acid (2.5 mL), and ethyl acetate (55 mL). The mixture was stirred to dissolve all solids and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 55 mL). The combined organic fractions were washed with saturated sodium bicarbonate solution and brine (20 mL each), dried (Na₂SO₄), and the solvent was evaporated under reduced pressure. The residue was triturated with hexane and the solid was collected and dried in vacuo to give 2,3-dihydro-3-hydroxyimino-1-methyl-5-phenyl-1H-pyrido[3,4-e]-1,4-diazepine-2-one (1.60 g, 100%) as a tan foam.

δ H (CDCl₃) 8.77 (1H, s), 8.50 (1H, d, J 4 Hz), 7.81 (2H, dd, J 8, 1 Hz), 7.60 (1H, m), 7.49 (3H, m), 7.32 (1H, d, J 5 Hz), and 3.55 (3H,s).

Step B:

A solution of stannous chloride dihydrate (3.72 g, 16.5 mmol) in concentrated hydrochloric acid (11 mL) was added dropwise to 2,3-dihydro-3-hydroxyimino-1-methyl-5-phenyl-1H-pyrido[3,4-e]-1,4-diazepine-2-one (1.54 g, 5.5 mmol) cooled in an ice bath. The resulting solution was stirred at ambient temperature for 3 h. The solution was diluted with water (20mL), basified with concentrated ammonium hydroxide (18 mL), and extracted with ether (4 x 75 mL). The combined organic fractions were washed with brine (30 mL), dried (Na₂SO₄), and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with methanol/chloroform/acetic acid (5:95:1 increasing to 10:90:1). The material which eluted was stirred under chloroform (20 mL) with potassium carbonate (0.3 g) and water (2 drops) for 5 min.

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The mixture was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was stirred under hexane, and the resulting solid was collected to give 3-amino-2,3-dihydro-1-methyl-5-phenyl-1H-pyrido[3,4-e]-1,4-diazepine-2-one (241 mg, 16%) as a yellow solid, m.p. 94-118°C.

δH (CDCl_3) 8.79 (1H, s), 8.48 (1H, d, J 5 Hz), 7.62 (2H, dd, J 8, 1 Hz), 7.51 (1H, m), 7.45 (2H, m), 7.24 (1H, dd, J 5, 1 Hz), 4.47 (1H, s), 3.55 (3H, s), and 2.2 (2H, bs).

Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O} \cdot 0.25(\text{C}_2\text{H}_5)_2\text{O}$:

C, 67.46; H, 5.84; N, 19.67.

Found: C, 67.28; H, 5.66; N, 19.53%.

High res. mass spectrum: Theoretical mass for $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}$ (M+1): 267.124586. Measured mass (M+1): 267.123093.

15 Step C:

A solution of oxalyl chloride (0.023 mL, 0.26 mmol) in methylene chloride (0.2 mL) was added dropwise to a solution of 3-(2,4-dichlorophenyl)propionic acid (48 mg, 0.22 mmol) and DMF (1 drop) in methylene chloride (0.5 mL) cooled in an ice-bath. The resulting solution was stirred 1 h. with cooling. The solvent was evaporated under reduced pressure to give 3-(2,4-dichlorophenyl)propionyl chloride (52 mg, 100%). To a solution of 3-amino-2,3-dihydro-1-methyl-5-phenyl-1H-pyrido[3,4-e]-1,4-diazepine-2-one (53 mg, 0.20 mmol) and pyridine (0.021 mL, 0.22 mmol) in methylene chloride (3 mL), was added a solution of 3-(2,4-dichlorophenyl)propionyl chloride (52 mg, 0.22 mmol) in methylene chloride (0.5 mL). The mixture was stirred for 1 h., the solvent was partially evaporated under reduced pressure, and the reaction mixture was purified by flash column chromatography on silica gel, eluting with methanol/ether (5:95 increasing to 7.5:92.5). The material which eluted was crystallized from toluene/hexane to give N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-pyrido[3,4-e]-1,4-diazepin-3-yl)-3-(2,4-dichlorophenyl)propanamide (38 mg, 38%) as a white crystalline solid, m.p. 220-221°C.

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δ H (CDCl₃) 8.81 (1H, s), 8.52 (1H, d, J 5 Hz), 7.56 (2H, dd, J 7, 2 Hz), 7.51 (1H, m), 7.44 (2H, d, J 6 Hz), 7.40 (1H, m), 7.27 (2H, m), 7.18 (2H, dd, J 8, 2 Hz), 5.48 (1H, d, J 8 Hz), 3.55 (3H, s), 3.10 (2H, t, J 7 Hz), and 2.71 (2H, dt, J_d 2 J_t 8 Hz).

5 Anal. Calcd. for C₂₄H₂₀Cl₂N₄O₂·0.25PhCH₃:

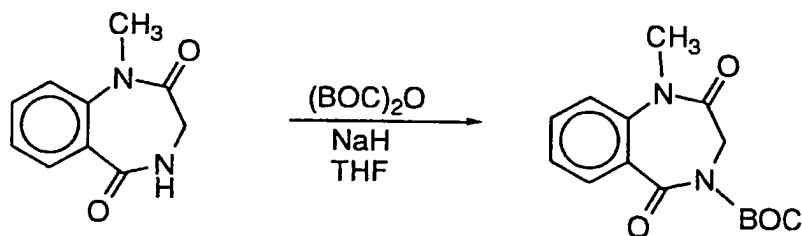
C, 63.06; H, 4.52; N, 11.43.

Found: C, 63.03; H, 4.48; N, 11.25%.

EXAMPLE 81

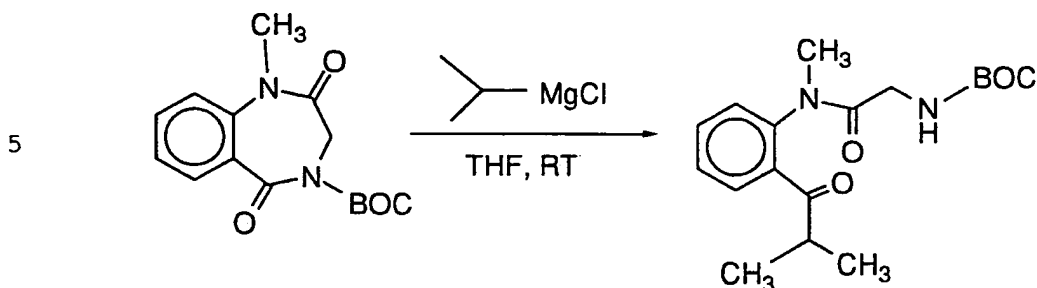
10 N-[2,3-Dihydro-1-methyl-2-oxo-5-isopropyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide

Step A:



To a solution of the benzodiazepine (1.0 g, 5.3 mmol) in THF (20 mL) at -78°C under argon was added 60% (NaH, 2.52 g, 6.3 mmol) Boc anhydride (1.27 g, 5.8 mmol) and the mixture stirred at
25 -78°C for 1/2 hour. The reaction was then allowed to warm to 25°C and stirred for 2 hours before quenching into cold aq. NH₄Cl (10%) and extracting the product into ethyl acetate (3x50 mL). Concentration of the dried (Na₂SO₄) extracts gave an oil which was passed through silica (EtOAc/hexane) to give 1.35 g product (89%).
30 ¹H NMR (CDCl₃) δ : 1.60 (s, 9H), 3.40 (s, 3H), 3.95 (brd, 1H), 4.80 (brd, 1H), 7.20 (d, 1H), 7.30 (q, 1H), 7.60 (t, 1H), 7.92 (d, 1H).

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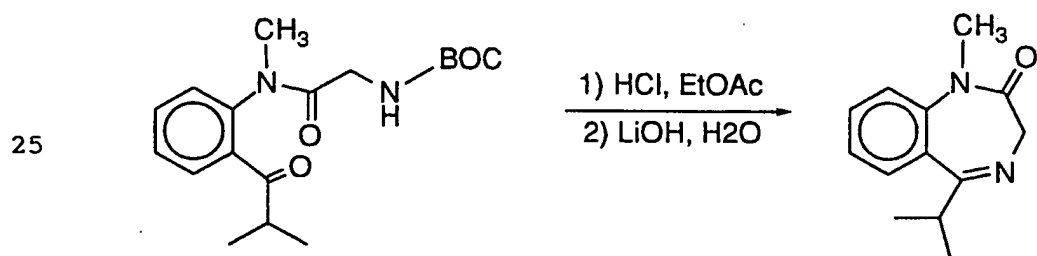
Step B:

10 To a solution of the BOC-benzodiazepine (4.0 g, 13.8 mmol) in THF (80 mL) under argon was rapidly added a solution of isopropylmagnesium chloride (2.0 M) in THF (7.66 mL, 15.3 mmol). The reaction was stirred for 1/2 hour, quenched into aq NH₄Cl (50 mL), and extracted with ethyl acetate (2x200 mL). The organic extracts

15 were concentrated and chromatographed on silica (1:1, EtOAc/hexane) to give 1.55 g (34%) of product.

¹H NMR (CDCl₃) δ: 1.14 (d, 3H), 1.19 (d, 3H), 1.40 (s, 9H), 3.13 (s, 3H), 3.2-3.8 (m, 3H), 5.45 (brs, 1H), 7.28 (dt, 1H), 7.48 (dt, 1H), 7.56 (dt, 1H), 7.72 (dd, 1H).

20

Step C:

30 To a 0°C solution of the isopropylphenone (1.55 g) in ethyl acetate was added anhydrous HCl gas over 90 min. The reaction was then concentrated in vacuo to give a solid which was dissolved in H₂O (40 mL) and the pH adjusted to 11.0 with 1N LiOH. After 30 min. at pH = 11.0 the pH was adjusted to 7.0 with 1N HCl and product extracted

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into ethyl acetate. The organic extracts were dried (Na₂SO₄), filtered and concentrated to give a solid 1.22 g, 100%.

¹H NMR (CDCl₃) δ: 0.95 (d, 3H), 1.30 (d, 3H), 3.16 (septet, 1H), 3.36 (s, 3H), 3.60 (d, 1H), 4.60 (d, 1H), 7.2-7.3 (m, 2H), 7.45-7.55 (m, 2H).

5

Step D:

The benzodiazepine obtained in Step C was converted to the oxime as described in Example 80 Step A.

10 Step E:

The oxime (2 gms) was dissolved in acetic acid (150 mL) and 10% Pd/C (1 gm) added. The mixture was stirred rapidly under an atmosphere of hydrogen for 90 min or until complete by HPLC. The reaction was filtered, the catalyst washed with methylene chloride (200 mL) and the filtrates concentrated in vacuo to an oil. The oil was dissolved in saturated aqueous sodium bicarbonate (100 mL) and product extracted with ethyl acetate (3 x 150 mLs). Concentration of the dried (Na₂SO₄) extracts gave 2.60 gms (97%).

20 Step F:

The anine was coupled with 3-(2,4-dichlorophenyl)-propionic acid as described in Example 43 to yield N-(2,3-dihydro-1-methyl-2-oxo-5-isopropyl-1H-1,4-benzodiazepin-3-yl)-3-(2,4-dichlorophenyl)propanamide.

25 ¹H NMR (CDCl₃) δ: 0.92 (d, 3H), 1.25 (d, 3H), 2.65 (dt, 2H), 3.05 (t, 2H), 3.15 (SepT, 1H), 3.40 (s, 3H), 5.38 (d, 1H), 7.0-7.6 (m, 8H).

The following compounds were prepared in a similar manner as described in Example 81, using the appropriate Grignard reagent in place of isopropyl magnesium chloride.

30

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EXAMPLE 82

N-[2,3-dihydro-1-methyl-2-oxo-5-isopropyl-1H-1,4-benzodiazepin-3-yl]-3-cyclohexylpropanamide

5 m.p. 164-165°C

CHN: Anal. Calcd. for C₂₂H₃₁N₃O₂:

C, 71.51; H, 8.46; N, 11.37

Observed: C, 71.72; H, 8.39; N, 11.32

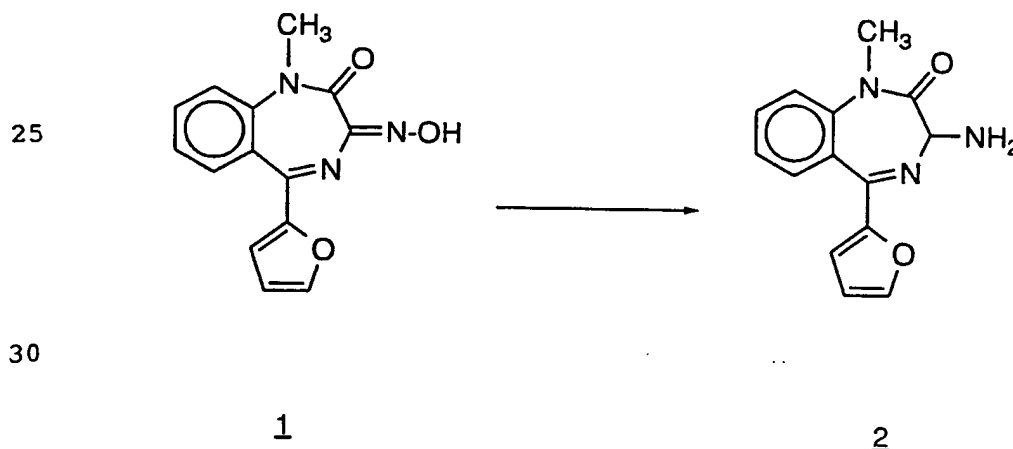
10 EXAMPLE 83

N-[2,3-dihydro-1-methyl-2-oxo-5-isopropyl-1H-1,4-benzodiazepin-3-yl]-3-(4-trifluoromethylphenyl)propanamide

m.p. 187-188°C

15 ¹H NMR (CDCl₃) δ: 0.92 (d, 3H), 1.25 (d, 3H), 2.66 (dt, 2H), 3.04 (t, 2H), 3.15 (SepT, 1H), 3.40 (s, 3H), 5.38 (d, 1H), 7.14 (brd, 1H), 7.25-7.6 (m, 8H).

Employing substantially the same methods described in
20 Example 80, but replacing Step E with the reduction method described below, the following compounds were prepared:



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- To a solution of the oxime 1 (1.28 g, 0.0048 mole) in H₂O (130 ml) and THF (65 ml) was added sodium dithionite (Na₂S₂O₄) (13.0 g, 0.075 mole). The mixture was stirred for 2 hours then diluted with saturated aqueous sodium bicarbonate (50 ml) and product
- 5 extracted into ethyl acetate (2 x 150 ml). The organic extracts were combined, dried over Na₂SO₄, filtered, and concentrated to give an oil (≈1.0 g). The oil was chromatographed on silica using ethyl acetate followed by 10% methanol/methylene chloride to give pure amine 0.778g (64%).
- 10 ¹H NMR (DMSO) δ 3.32 (s, 3H), 4.30 (s, 1H), 6.64 (d, d, 1H), 6.76 (d, 1H), 7.35 (dt, 1H), 7.58-7.74 (m, 3H), 7.88 (m, 1H).

EXAMPLE 84

- 15 N-[2,3-dihydro-1-methyl-2-oxo-5-(2-furanyl)-1H-1,4-benzodiazepin-3-yl]-3-cyclohexylpropanamide
m.p. 168-169°C
CHN: Anal. Calcd. for C₂₃H₂₇N₃O₃:
C, 70.21; H, 6.92; N, 10.68
- 20 Observed: C, 70.15; H, 6.67; N, 10.64

EXAMPLE 85

- 25 N-[2,3-dihydro-1-methyl-2-oxo-5-(2-furanyl)-1H-1,4-benzodiazepin-3-yl]-3-(4-trifluoromethylphenyl)propanamide
m.p. 155-157°C
CHN: Anal. Calcd. for C₂₄H₂₀N₃O₃F₃:
C, 63.29; H, 4.432; N, 9.23
- Observed: C, 63.22; H, 4.44; N, 9.07

30

EXAMPLE 86

N-[2,3-dihydro-1-methyl-2-oxo-5-(2-furanyl)-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide

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m.p. 132-133°C

CHN: Anal. Calcd. for C₂₃H₁₉N₃O₃Cl₂

C, 60.54; H, 4.20; N, 9.21

Found: C, 60.62; H, 4.07; N, 9.07

5

EXAMPLE 87

N-[2,3-dihydro-1-methyl-2-oxo-5-(3-furanyl)-1H-1,4-benzodiazepin-3-yl]-3-cyclohexylpropanamide

10 m.p. 199-200°C

¹H NMR (CDCl₃) δ: 0.9-1.8 (brm, 3H), 2.38 (t, 2H), 3.42 (s, 3H), 5.55 (brd, 1H), 6.90 (s, 1H), 7.2-7.77 (m, 7H)

EXAMPLE 88

15

N-[2,3-Dihydro-1-methyl-2-oxo-5-(3-furanyl)-1H-1,4-benzodiazepin-3-yl]-3-(4-trifluoromethylphenyl)propanamide

m.p. 213-214°C

¹H NMR (CDCl₃) δ: 2.71 (dt, 2H), 3.05 (t, 2H), 3.42 (s, 3H), 5.72 (d, 20 1H), 6.82 (brs, 1H), 7.2-7.7 (m, 11H)

EXAMPLE 89

N-[2,3-Dihydro-1-methyl-2-oxo-5-[2'-(4,4-dimethyl-2-oxazolinyl)-phenyl]-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)-propanamide

The subject compound was prepared substantially as described in Example 81.

30 m.p. 194-195°C

CHN: Anal. Calcd. for C₃₀H₂₈N₄O₃Cl₂

C, 63.95; H, 5.01; N, 9.94

Found: C, 63.70; H, 5.01; N, 9.96

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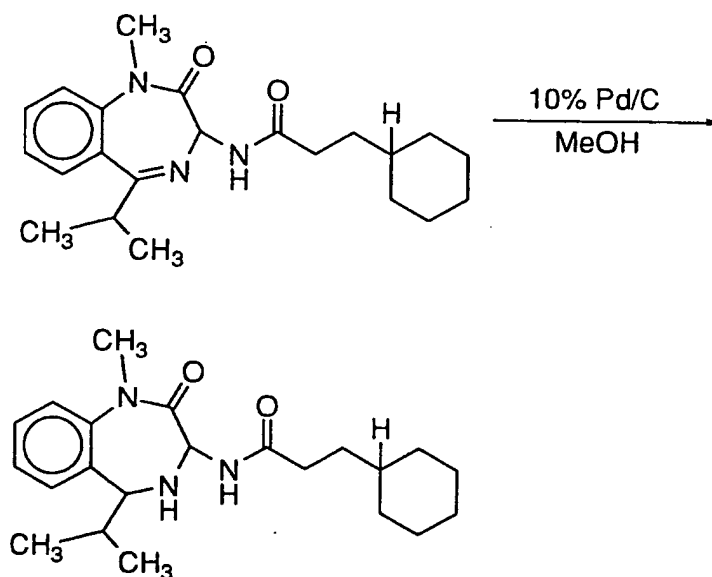
EXAMPLE 90

N-[2,3,4,5-Tetrahydro-1-methyl-2-oxo-5-isopropyl-1H-1,4-benzodiazepin-3-yl]-3-cyclohexylpropanamide

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A solution of N-[2,3-dihydro-1-methyl-2-oxo-5-isopropyl-1H-1,4-benzodiazepin-3-yl]-3-cyclohexylpropanamide (50 mg) in methanol (10 mL), containing 10% Pd/C (50 mg) was stirred under 1 atmosphere of hydrogen for 18 hours. Filtration of the reaction, concentration and crystallization from diethyl ether gave 21 mg N-[2,3,4,5-tetrahydro-1-methyl-2-oxo-5-isopropyl-1H-1,4-benzodiazepin-3-yl]-3-cyclohexylpropanamide.

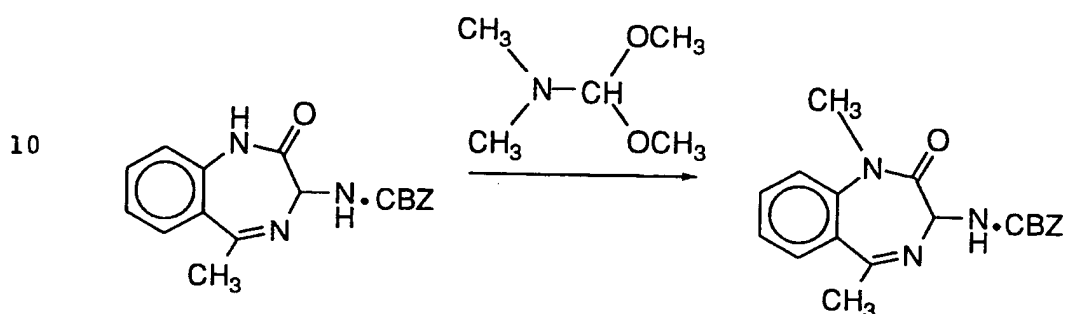
30

CHN: Anal. Calcd. for C₂₂H₃₃N₃O₂
C, 71.12; H, 8.95; N, 11.31
Observed: C, 70.98; H, 8.97; N, 11.15
m.p. 114-115°C

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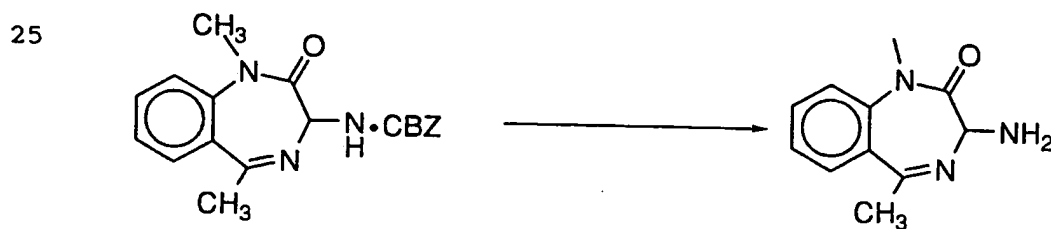
EXAMPLE 91

N-[2,3-dihydro-1-methyl-2-oxo-5-methyl-1H-1,4-benzodiazepin-3-yl]-
3-(2,4-dichlorophenyl)propanamide

Step A:

To CBZ-benzodiazepine (250 mg, 0.776 mmol) in toluene (25 mL) at reflux was added dropwise a solution of DMF dimethylacetal (1.09 mL) in toluene (10 mL). The reaction was refluxed for 5 hours, cooled and concentrated to an oil. The oil was triturated with ether to give a white solid (124 mg).

¹H NMR (CDCl₃) δ: 2.50 (s, 3H), 3.42 (s, 3H), 5.12-5.20 (m, 3H), 6.62 (d, 1H), 7.25-6.4 (m, 7H), 7.5-7.6 (m, 2H).

Step B:

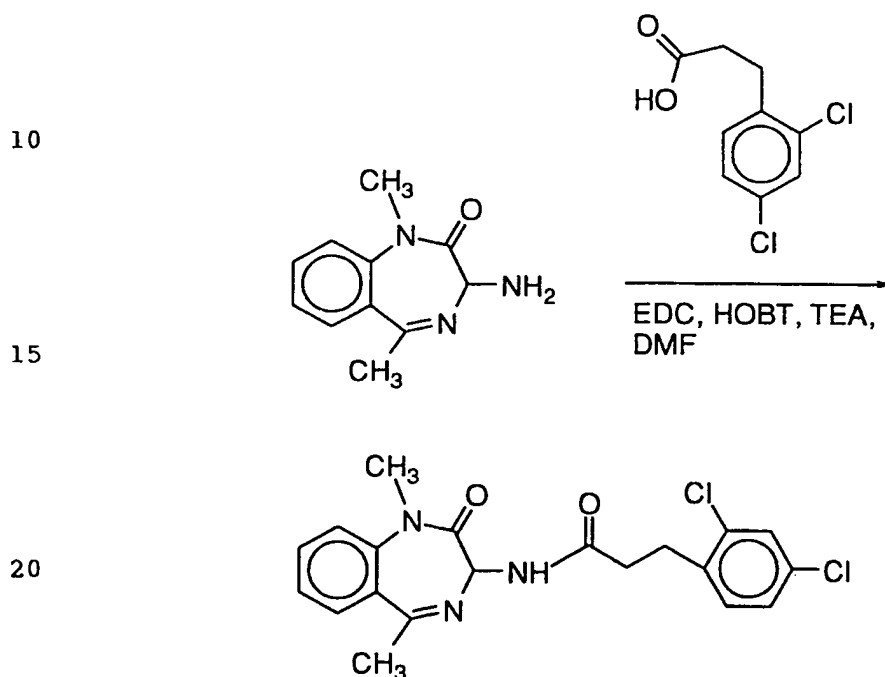
The CBZ-amine-N-methyl amide (190 mg) was treated with 30% HBr/AcOH (0.8 mL) for 1 hour at room temperature. The reaction mixture was poured into ether (10 mL) at 0°C and the solid filtered. Solid dissolved in 10% Aq. NaOH (5 mL) and CH₂Cl₂ (10

- 132 -

mL) and organic layer separated, dried (Na₂SO₄), filtered and concentrated to an oil (172 mg, 110%).

¹H NMR (CDCl₃) δ: 2.42 (s, 3H), 3.05 (brs, 2H), 3.40 (s, 3H), 4.40 (s, 1H), 7.2-7.6 (m, 4H).

5
Step C:



25 N-[2,3-dihydro-1-methyl-2-oxo-5-methyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide was prepared in a similar manner as described previously in Example 43.

m.p. 194-195°C

CHN: Anal. Calcd. for C₂₀H₁₉N₃O₂Cl₂

C, 59.42; H, 4.74; N, 10.39

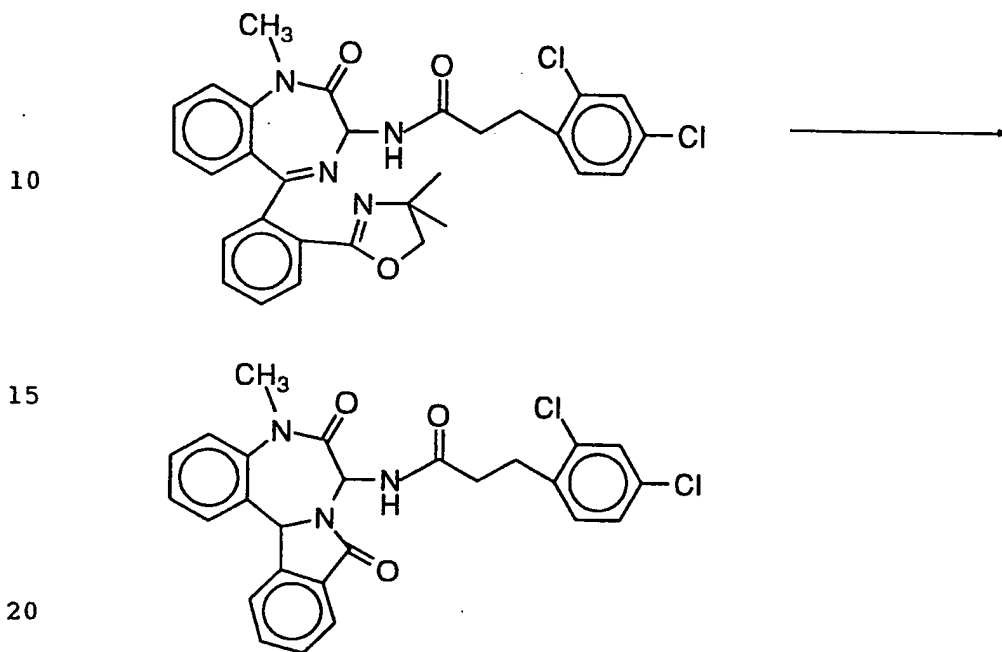
30 Observed: C, 59.50; H, 4.74; N, 10.44

¹H NMR (CDCl₃) δ: 2.49 (brs, 3H), 2.65 (dt, 2H), 3.05 (t, 2H), 3.42 (s, 3H), 5.35 (d, 1H), 7.1-7.6 (m, 8H).

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EXAMPLE 92

N-[2,3-Dihydro-1-methyl-2-oxo-[4,5-a]-(1-oxo-1,3-dihydro-2H-
 isoindole)-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)-
 5 propanamide



To a solution of N-[2,3-dihydro-1-methyl-2-oxo-5-[2'-(4,4-
 dimethyl-2-oxazolinyl)phenyl]-1H-1,4-benzodiazepin-3-yl]-3-(2,4-
 25 dichlorophenyl)propanamide (100 mg, 0.178 mmol) in methylene
 chloride was slowly added methyl trifluoromethanesulfonate (22 mL,
 0.198 mmol). After stirring 5 minutes, sodium borohydride (7.6 mg,
 0.20 mmol) in absolute ethanol (0.5 mL) was added and reaction stirred
 30 min. the product was extracted into ethyl acetate and purified by
 column chromatography on silica (60% ethyl acetate/hexane) to give 30
 mg N-[2,3-dihydro-1-methyl-2-oxo-[4,5-a]-(1-oxo-1,3-dihydro-2H-
 isoindole)-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)-
 propanamide.

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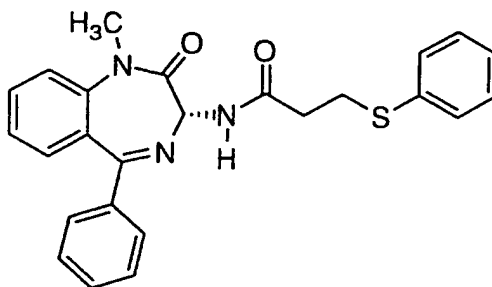
^1H NMR (CDCl_3) δ : 2.70 (m, 2H), 3.12 (t, 2H), 3.55 (s, 3H), 5.68 (s, 1H), 5.90 (d, 1H), 6.85 (dd, 1H), 7.05 (brd, 1H), 7.1-7.5 (m, 9H), 7.85 (d, 1H).

MS $\text{M}+1$ -494.

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EXAMPLE 93

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3R-(+)-3-(Phenylthio)-N-[2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]propanamide

To a stirred solution of 3-bromopropionic acid (1.0g, 6.5mmol) in DMF (20 mL) was added K_2CO_3 (1.8 g, 13 mmol) and thiophenol (0.72 g, 6.5 mmol). This was heated to 50°C for 1h. The mixture was then diluted with 200 mL H_2O and extracted with 2 x 100 mL EtOAc. The combined organics were washed with 100 mL H_2O and dried with Na_2SO_4 . This was evaporated to give 1.52g of a colorless oil, 1.18g corrected for residual DMF by NMR.

25

The above oil was taken up in 30 mL DMF and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.45g, 12.8mmol) and 1-hydroxybenzotriazole hydrate (1.73g, 12.8mmol) were added. This was stirred for 5 min at rt. 3-(R)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (0.66g, 2.6mmol) was then added and the reaction was stirred at rt overnight. The reaction was diluted with 200 mL H_2O and extracted with 2x150mL EtOAc. The combined organics were washed with 1x100mL H_2O , dried with Na_2SO_4 and evaporated. The residue was chromatographed over silica eluting with 2% MeOH: CHCl_3 . Collected

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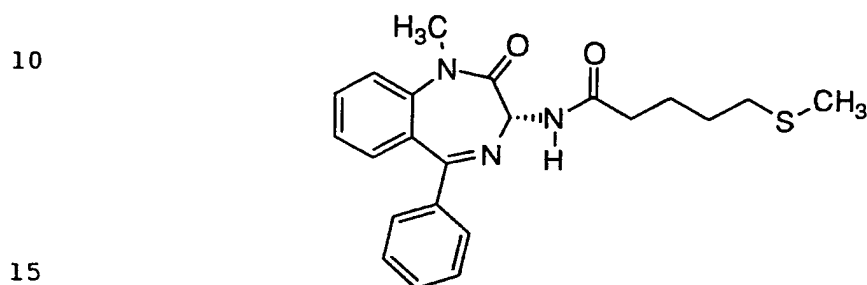
pure fractions, evaporated. Evaporated from diethyl ether to give 770mg of a white foam.

Anal. Calcd for $C_{25}H_{23}N_3O_2S \cdot 0.05\text{Hexane}$:

C, 70.04; H, 5.51; N, 9.69.

5 Found: C 69.91, H 5.40, N 9.78.

EXAMPLE 94



3R-(+)-5-(Methylthio)-N-[2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]propanamide

20 To an aqueous solution of K_2CO_3 (0.76g, 5.5mmol) was added 5-bromopentanoic acid and sodium thiomethoxide. This was stirred at rt overnight. The reaction was diluted with 50 mL H_2O and acidified to pH=0 with 6N HCl. Extracted with 2 x 50 mL EtOAc. Dried with Na_2SO_4 , evaporated to give 0.55g of a yellow oil.

25 The above oil was taken up in 10 mL DMF and 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (1.30g, 6.8mmol) and 1-hydroxybenztriazole hydrate (0.92g, 6.8mmol) were added. 3-(R)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (0.85g, 3.4mmol) was then added and the reaction
30 was stirred overnight at rt. The reaction was diluted with 100 mL H_2O and extracted with 2 x 50 mL EtOAc. Combined organics were dried with brine and Na_2SO_4 , and evaporated to give yellow oil. The residue was chromatographed over silica eluting with 50:50 EtOAc:Hex to 100% EtOAc. Pure fractions were collected to give 1.33g of a colorless oil, 0.4g of which was chromatographed over silica eluting

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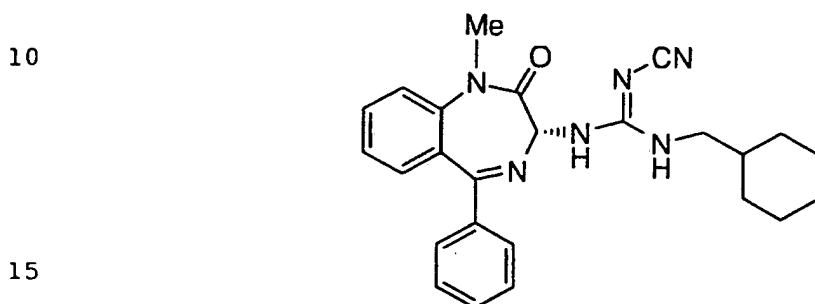
with 2% MeOH:CH₂Cl₂. Pure fractions were collected, and evaporated from ethyl ether:hexane to give a white powder mp. 61-65°C.

Anal. Calcd for C₂₂H₂₅N₃O₂S•0.35H₂O:

C, 65.76; H, 6.45; N, 10.46.

5 Found: C, 65.81; H, 6.21; N, 10.57.

EXAMPLE 95



N-cyano-N'-cyclohexylmethyl-N''-(1,3-dihydro-1-methyl-2-oxo-5-phenyl-2H-1,4-benzodiazepin-3-yl)guanidine

20 A solution of 3-(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (1g, 3.7 mmole) in acetonitrile (20 mL) was treated with diphenylcyanocarbonimide (0.9 g, 3.7 mmole) and stirred at room temperature for thirty minutes. Cyclohexylmethylamine (0.84 g, 7.4 mmole) was then added and the reaction stirred at

25 room temperature for two hours. The reaction was poured into 100 mL of 0.1 N HCl and extracted with 3 x 100 mL portions of ethyl acetate. The organic layers were combined and washed once with saturated sodium bicarbonate (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure. The

30 residue was chromatographed on silica gel eluting with 50% ethyl acetate/hexane to give 0.875 g of the product. The analytical sample was crystallized from ethyl acetate.

m.p. 158-161°C.

Anal. Calcd. for C₂₅H₂₈N₆O:

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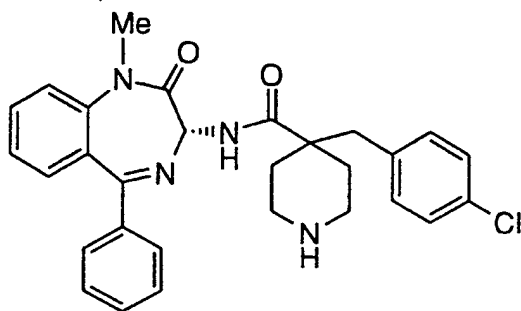
C, 70.07; H, 6.59; N, 19.61.

Found: C, 70.05; H, 6.59; N, 19.64%.

EXAMPLE 96

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N-(1,3-Dihydro-1-methyl-2-oxo-5-phenyl-2H-1,4-benzodiazepin-3-yl)-4-(4-chlorobenzyl)-4-piperidinecarboxamide dihydrochloride

Step A: Preparation of N-tert-butyloxycarbonyl-4-(4-chlorobenzyl)-4-piperidinecarboxylic acid

20

A solution of N-Boc-ethylisonipecotate (51.4 g, 200 mmole) in THF (1L) at -60° C was treated with a solution of lithium bistrimethylsilyl amide (220 mL of a 1 N solution in THF, 220 mmole). After stirring at -60°C for 5 minutes, a solution of 4-chlorobenzyl chloride (33.8 g, 210 mmole) in THF (200 mL) was added and the reaction allowed to warm to room temperature. Most of the THF (about 800 mL) was removed by evaporation at reduced pressure. The remainder was poured into 1 L of 1 N HCl and extracted with two 800 mL portions of ethyl acetate. The organic layers were combined and washed once with saturated sodium bicarbonate (500 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 10%-20% ethyl acetate/hexane to give the product ester which was used directly. The material thus obtained was dissolved in THF (100 mL) and IPA (100 mL) and treated with 350 mL of 10 N NaOH. The mixture was heated to reflux for 30 hours. The reaction was cooled to

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room temperature and poured over a mixture of crushed ice (2 L), 6 N HCl (500 mL) and saturated potassium hydrogen sulfate (1 L). The mixture was extracted with two 1 L portions of ethyl acetate. The organic layers were combined and dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure to give 52 g of the product.

m.p. 179-180°C,

^1H NMR CDCl_3 δ 7.26 (d, J = 8 Hz, 2 H), 7.03 (d, J = 8 Hz, 2 H), 3.98 (m, 2H), 3.0-2.8 (m, 2H), 2.84 (s, 2H), 2.10-2.00 (m, 2H), 1.55-1.40 (m, 2H), 1.45 (s, 9H)

Step B: Preparation of N-(1,3-dihydro-1-methyl-2-oxo-5-phenyl-2H-1,4-benzodiazepin-3-yl)-4-(4-chlorobenzyl)-4-piperidinecarboxamide dihydrochloride

A mixture consisting of N-tert-butyloxycarbonyl-4-(4-chlorobenzyl)-4-piperidinecarboxylic acid (1.48 g, 4.18 mmole), 3-(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (1g, 3.7 mmole), hydroxybenzotriazole (1.17 g, 8.66 mmole), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.49 g, 7.70 mmole), diisopropylethyl amine (0.53 g, 4.13 mmole), and DMF (10 mL) was stirred at room temperature for 18 hours. The reaction was poured into 1 N HCl and extracted with ethyl acetate (4 X 50 mL). The organic layers were combined and washed once with saturated sodium bicarbonate (50 mL), once with saturated sodium chloride (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 25%-50% ethyl acetate/hexane to give 2.34 g of the product amide which was used directly. The material thus obtained was dissolved in ethyl acetate (50 mL) and HCl (g) was bubbled into the reaction for 5 minutes. The reaction was concentrated at reduced pressure and the residue recrystallized from ethyl acetate to give 1.13 g of the product as a pale yellow solid.

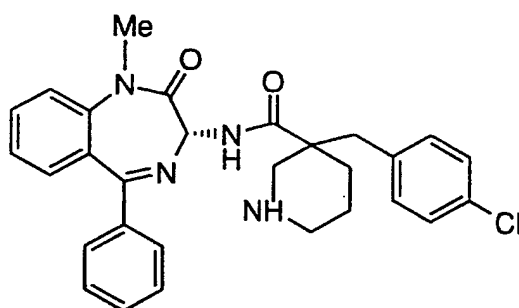
m.p. 190 - 195°C.

Anal. Calcd. for $\text{C}_{29}\text{H}_{29}\text{ClN}_4\text{O}_2 \cdot 2 \text{HCl}$:

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Found: C, 60.68; H, 5.44; N, 9.76.
C, 60.47; H, 5.5; N, 9.42%.

Utilizing the procedures substantially as described above
except substituting N-Boc-ethylnipeotate for N-Boc-ethyl isonipecotate
there were obtained the following compounds

EXAMPLE 97

N-(1,3-dihydro-1-methyl-2-oxo-5-phenyl-2H-1,4-benzodiazepin-3-yl)-
3-(4-chlorobenzyl)-3-piperidinecarboxamide hydrochloride A + B
isomers

Isomer A

m.p. 205 - 210°C.

Anal. Calcd. for $C_{29}H_{28}ClN_4O_2 \cdot HCl \cdot 0.5 CH_3CH_2OH \cdot 0.8 H_2O$:

C, 62.67; H, 6.07; N, 9.75.

Found: C, 62.69; H, 5.94; N, 9.42%.

Isomer B

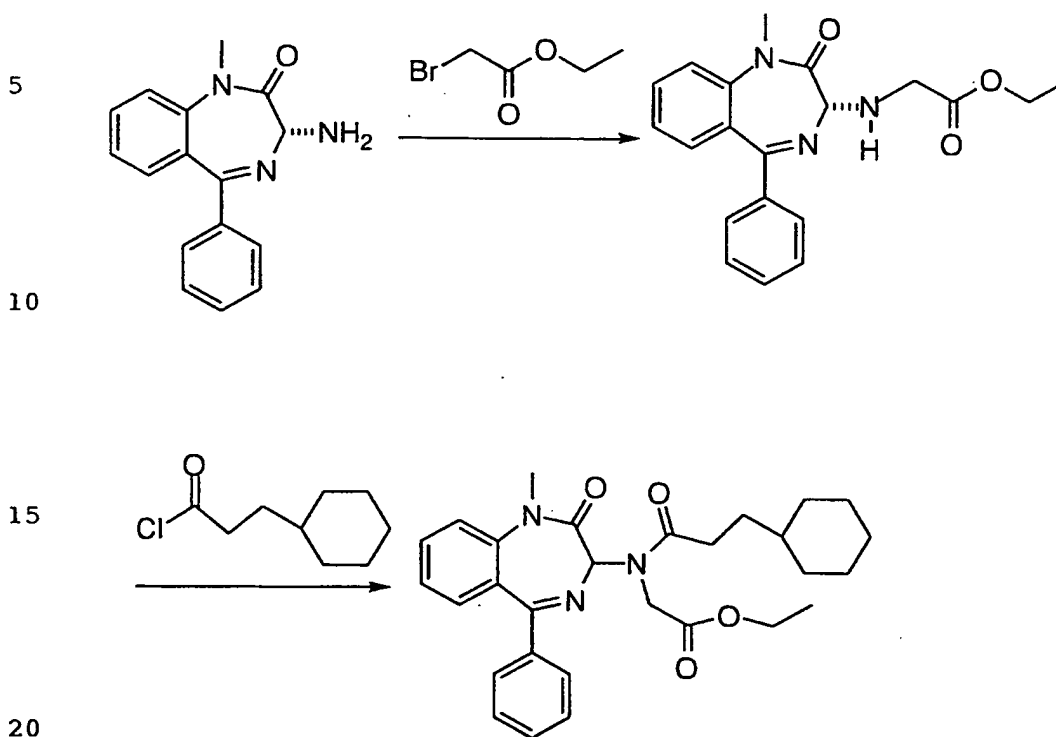
m.p. 200 - 205°C.

Anal. Calcd. for $C_{29}H_{28}ClN_4O_2 \cdot HCl \cdot 0.1 CH_3CH_2OCOCH_3 \cdot 1.6 H_2O$:

C, 61.39; H, 5.96; N, 9.74.

Found: C, 61.39; H, 5.66; N, 9.56%.

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EXAMPLE 98

(+)-3-Cyclohexyl-N-[2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N-(ethoxycarbonylmethyl)propanamide

3-(R)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (5.0 g, 18.8 mmol) in acetonitrile (100 mL) was mixed with ethyl bromoacetate (2.1 mL, 18.8 mmol) and sodium hydrogen carbonate (4.0 g) was suspended in the mixture. The mixture was stirred and heated at reflux for 2 h. After that time, the reaction was cooled to room temperature, diluted with 150 mL water, and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried with magnesium sulfate, gravity filtered, and the solvent was removed in vacuo. The resulting oil was chromatographed over silica in 3:1 ethyl acetate:hexane, yielding the mono-alkylated product (2.58 g, 39%) as well as the starting 1,4-benzodiazepin-2-one

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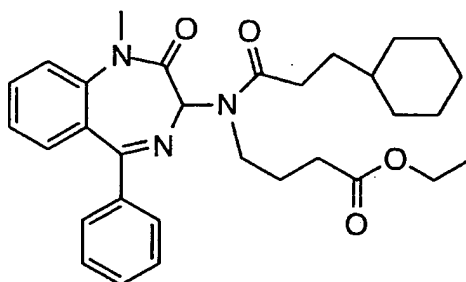
and bis-alkylated material. To a solution of 3-cyclohexylpropionic acid (1.0 g, 6.40 mmol) in methylene chloride (30 mL) was added oxalyl chloride (0.56 mL, 6.40 mmol) and catalytic (N,N)-dimethyl formamide (2 drops). After 0.5 h, a solution of the acetate (2.25 g, 6.40 mmol) in methylene chloride (10 mL) was added and the reaction was stirred for 0.25 h. The reaction was then diluted with methylene chloride (150 mL) and saturated aqueous sodium hydrogen carbonate (150 mL) was added. The aqueous portion was extracted again with methylene chloride (2 x 100 mL) and the organics were combined, dried with magnesium sulfate, gravity filtered, and the solvent was removed in vacuo. The resulting oil was chromatographed over silica with 1:1 ethyl acetate:hexane, yielding a foam that was crystallized with ether, giving 2.0 g (64%) of the product.
m.p. 120-122°C, $[\alpha]_D + 0.63^\circ$ (c=0.79; MeOH).
Anal. Calcd. for $C_{29}H_{35}N_3O_4$:
C, 71.14; H, 7.21; N, 8.58.
Found: C, 71.13; H, 7.13; N, 8.75%.

The following compound was prepared in a manner substantially as described above except substituting ethyl bromobutyrate for ethyl bromoacetate.

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EXAMPLE 99

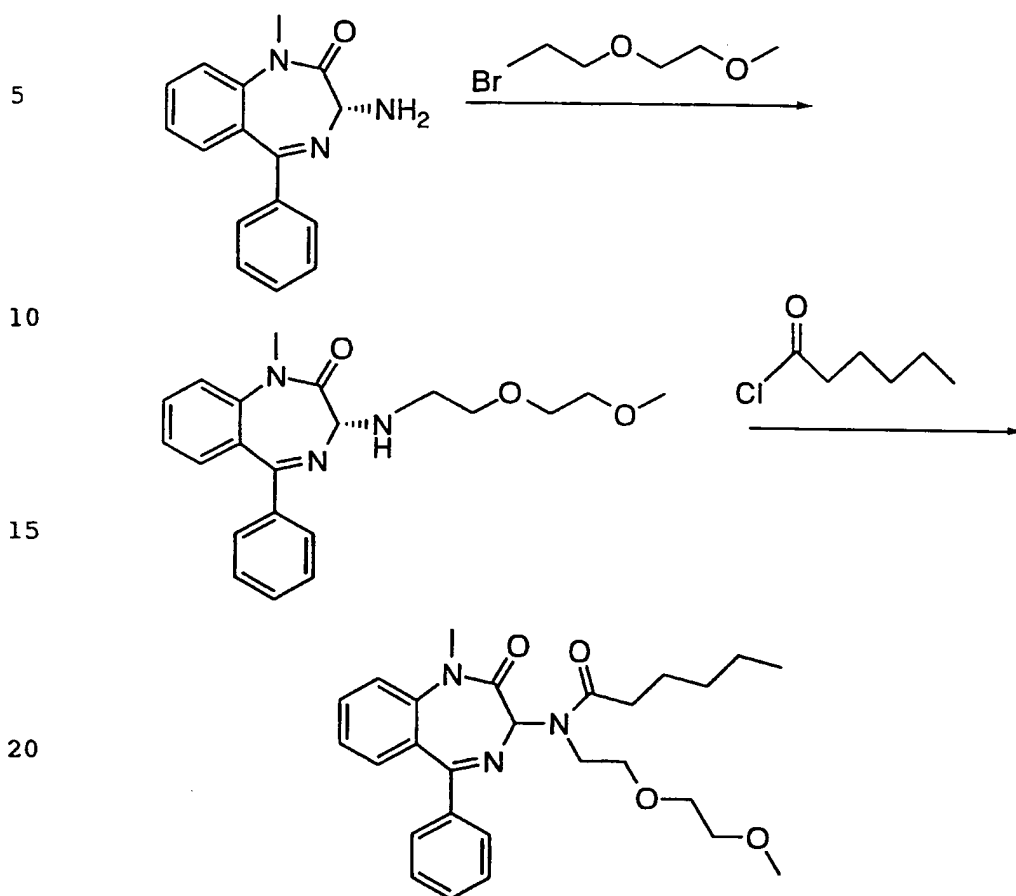
3-Cyclohexyl-N-[2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N-(ethoxycarbonylpropyl)propanamide
m.p. 103-105°C, $[\alpha]_D^{25}$ 0.00°; $c=0.85$; MeOH.

Anal. Calcd. for $C_{31}H_{39}N_3O_4 \cdot 0.40$ mol H_2O :

C, 70.94; H, 7.64; N, 8.01.

Found: C, 70.91; H, 7.44; N, 8.12%.

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EXAMPLE 100

25 N-[2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-
N-[2-(2-methoxyethoxy)ethyl]hexanamide

3-(R)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (1.33 g, 5.0 mmol) in N,N-dimethyl formamide (30 mL) was mixed with 1-bromo-2-(2-methoxyethoxy)ethane (1.35 mL, 5.0 mmol) and triethylamine (1.0 mL). The mixture was stirred and heated at reflux for 4 h. After that time, the reaction was cooled to room temperature, diluted with 150 mL water, and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried with magnesium sulfate, gravity filtered, and the solvent was removed in

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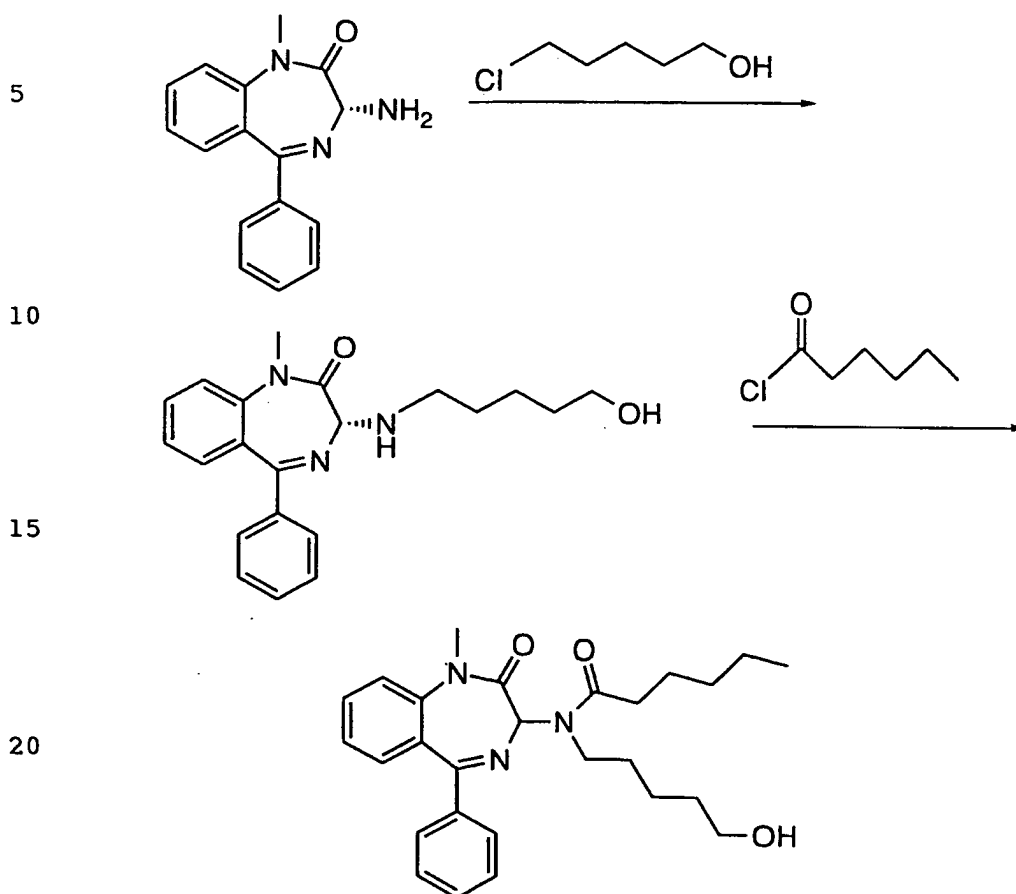
vacuo. The resulting oil was chromatographed over silica in 1:1 ethyl acetate:hexane, yielding the mono-alkylated product (1.2 g, 65%) as well as the starting 1,4-benzodiazepin-2-one and bis-alkylated material. To a solution of the mono-alkylated material (1.2 g, 3.27 mmol) in
5 methylene chloride (20 mL) was added hexanoyl chloride (0.96 mL, 3.27 mmol) and the reaction was stirred for 0.25 h. The reaction was then diluted with methylene chloride (150 mL) and saturated aqueous sodium hydrogen carbonate (150 mL) was added. The aqueous portion was extracted again with methylene chloride (2 x 100 mL) and the
10 organics were combined, dried with magnesium sulfate, gravity filtered, and the solvent was removed in vacuo. The resulting oil was chromatographed over silica with 1:1 ethyl acetate:hexane, yielding an oil, giving 580 mg (38%) of the product.
[α]_D 0.00°; c=0.27; MeOH.
15 Anal. Calcd. for C₂₇H₃₅N₃O₄•0.80 mol H₂O:
C, 67.56; H, 7.69; N, 8.75.
Found: C, 67.56; H, 7.39; N, 8.85%.

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EXAMPLE 101

25 (+)-N-[2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N-(5-hydroxypentyl)hexanamide

30 3-(R)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (1.33 g, 5.0 mmol) in acetonitrile (40 mL) was mixed with 5-chloropentan-1-ol (0.61 g, 5.0 mmol) and sodium hydrogen carbonate (2.0 g) was suspended in the mixture. The mixture was stirred and heated at reflux for 12 h. After that time, the reaction was cooled to room temperature, diluted with 100 mL water, and extracted with ethyl acetate (3 x 75 mL). The organic layers were combined, dried with magnesium sulfate, gravity filtered, and the

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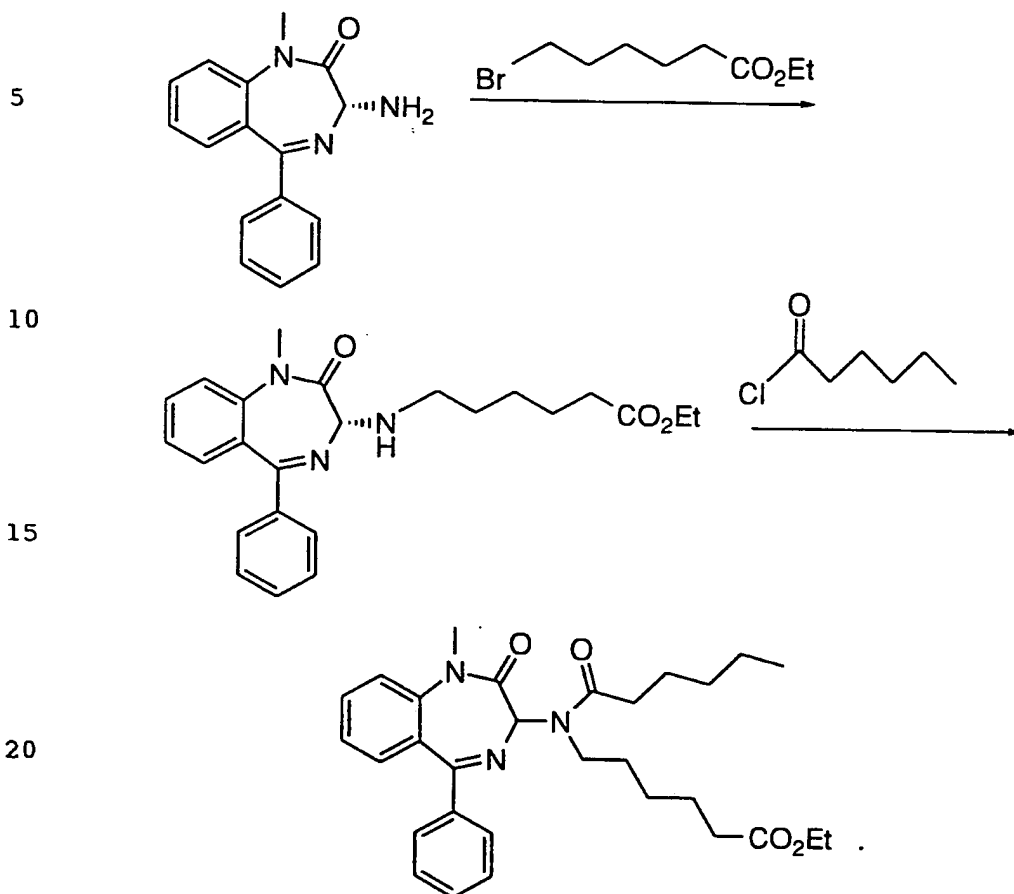
solvent was removed in vacuo. The resulting oil was chromatographed over silica in 1:49 methanol:chloroform yielding the mono-alkylated product (1.1 g, 62%) as well as the starting 1,4-benzodiazepin-2-one and bis-alkylated material. To a solution of the monoalkylated material (0.50 g, 1.42 mmol) in methylene chloride (30 mL) was added hexanoyl chloride (0.20 mL, 1.42 mmol) and the reaction was stirred for 0.25 h. The reaction was then diluted with methylene chloride (100 mL) and saturated aqueous sodium hydrogen carbonate (100 mL) was added. The aqueous portion was extracted with methylene chloride (2x75 mL) and the organics were combined, dried with magnesium sulfate, gravity filtered, and the solvent was removed in vacuo. The resulting oil was chromatographed over silica with 1:1 ethyl acetate:hexane, yielding a foam, giving 360 mg (64%) of the product. foam , $[\alpha]_D + 8.36^\circ$ (c=0.61, MeOH).

Anal. Calcd. for $C_{27}H_{35}N_3O_2 \cdot 0.25 \text{ mol H}_2O$:

C, 71.42; H, 7.88; N, 9.25.

Found: C, 71.47; H, 7.89; N, 9.12%.

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EXAMPLE 102

25 (+)-N-[2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N-(ethoxycarbonylpentyl)hexanamide

30 3-(R)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (1.33 g, 5.0 mmol) in acetonitrile (40 mL) was mixed with ethyl-6-bromohexanoate (0.89 mL, 5.0 mmol) and sodium hydrogen carbonate (2.0 g) was suspended in the mixture. The mixture was stirred and heated at reflux for 10 h. After that time, the reaction was cooled to room temperature, diluted with 100 mL water, and extracted with ethyl acetate (3x75 mL). The organic layers were combined, dried with magnesium sulfate, gravity filtered, and the

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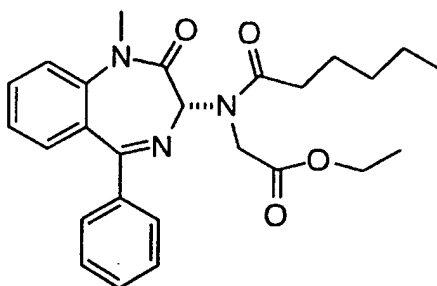
solvent was removed in vacuo. The resulting oil was chromatographed in 1:49 methanol:chloroform, yielding the mono-alkylated product (0.56 g, 28%) as well as the starting 1,4-benzodiazepin-2-one and bis-alkylated material. To a solution of the mono-alkylated material (0.56 g, 1.37 mmol) in methylene chloride (20 mL) was added hexanoyl chloride (0.19 mL, 1.37 mmol) and the reaction was stirred for 0.25 h. The reaction was then diluted with methylene chloride (100 mL) and saturated aqueous sodium hydrogen carbonate (100 mL) was added. The aqueous portion was extracted again with methylene chloride (2x75 mL) and the organics were combined, dried with magnesium sulfate, gravity filtered, and the solvent was removed in vacuo. The resulting oil was chromatographed over silica with 1:1 ethyl acetate:hexane, yielding a foam, giving 0.40 g (58%) of the product. m.p. 59-65°C, $[\alpha]_D^{25}$ (+)52.7° (c=0.48, MeOH).
Anal. Calcd. for C₃₀H₃₉N₃O₄•0.20 mol CH₂Cl₂:
C, 69.4; H, 7.6; N, 8.04.
Found: C, 69.44; H, 7.68; N, 7.71%.

The following compound was prepared in a manner substantially as described above except substituting ethyl bromoacetate for ethyl 6-bromohexanoate.

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EXAMPLE 103

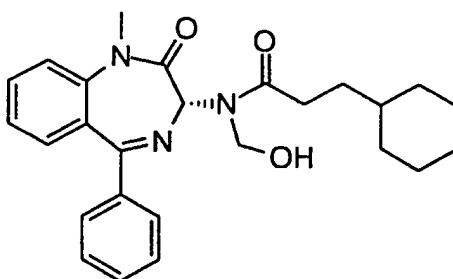
(+)-N-[2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N-(ethoxycarbonylmethyl)hexanamide

foam, $[\alpha]_D + 2.04^\circ$ (c=0.98; MeOH).

Anal. Calcd. for $C_{26}H_{31}N_3O_4$:

C, 69.47; H, 6.95; N, 9.35.

Found: C, 69.41; H, 7.03; N, 9.26%.

EXAMPLE 104

(+)-3-Cyclohexyl-N-[2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N-(hydroxymethyl)propanamide

(+)-3-Cyclohexyl-N-[2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]propanamide (2.0 g, 5.0 mmol) was dissolved in tetrahydrofuran (30 mL), cooled to 0°C and methyl magnesium chloride (3M, 2.0 mL) was added. After 0.25 h,

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paraformaldehyde (0.15 g, 10 mmol) was added, and the mixture was allowed to warm to room temperature. The reaction was then diluted with ethyl acetate (150 mL) and saturated aqueous sodium hydrogen carbonate (150 mL) was added. The aqueous portion was extracted again with ethyl acetate (2 x 100 mL) and the organics were combined, dried with magnesium sulfate, gravity filtered, and the solvent was removed in vacuo. The resulting oil was chromatographed over silica with 1:1 ethyl acetate:hexane, yielding a foam (0.80 g, 37%). foam, $[\alpha]_D + 124^\circ$ ($c=0.69$, MeOH).

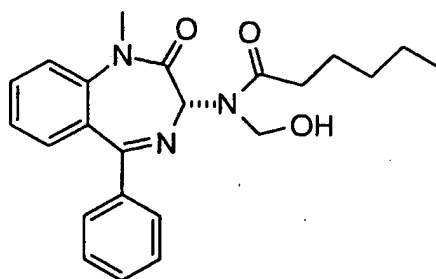
Anal. Calcd. for $C_{26}H_{31}N_3O_3$:

C, 72.03; H, 7.21; N, 9.69.

Found: C, 71.66; H, 7.08; N, 9.78%.

The following compound was prepared in a manner substantially as described above starting from (+)-N-[2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]hexanamide.

EXAMPLE 105



(+)-N-[2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N-(hydroxymethyl)hexanamide

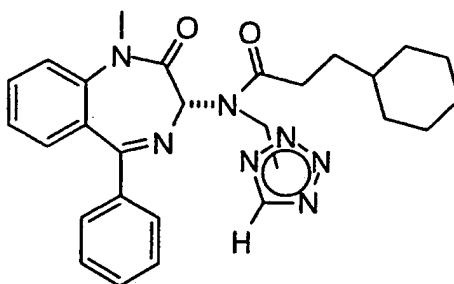
m.p. 154-156°C, $[\alpha]_D + 190.8^\circ$ ($c=0.24$, MeOH).

Anal. Calcd. for $C_{23}H_{27}N_3O_3 \cdot 0.30 \text{ mol H}_2\text{O}$:

C, 69.26; H, 6.97; N, 10.53.

Found: C, 69.29; H, 6.81; N, 10.6%.

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EXAMPLE 106

(+)-3-Cyclohexyl-N-[2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N-(tetrazolylmethyl)propanamide

(+)-3-Cyclohexyl-N-[2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N-(hydroxymethyl)propanamide (0.67 g, 1.56 mmol) was dissolved in methylene chloride (100 mL), along with tetrazole (0.33 g, 4.7 mmol), and then N,N-diisopropyl-dibenzyl-phosphoramidite (1.07 g, 3.1 mmol). After 2 h, the mixture was diluted with methylene chloride (150 mL), and extracted with saturated aqueous sodium hydrogen carbonate (3 x 100 mL). The organic layers were combined, dried with magnesium sulfate, gravity filtered, and the solvent was removed in vacuo. The resulting oil was chromatographed twice over silica with 1:1 ethyl acetate:hexane, yielding two constitutional isomers, a (65 mg, 9%) and b (56 mg, 7.5%).

Isomer A:

m.p. 96-98°C, $[\alpha]_D^{25} +188.9^\circ$ (c=0.19, MeOH).

Anal. Calcd. for C₂₇H₃₁N₇O₂•0.30 mol TFA:

C, 63.78; H, 6.07; N, 18.86.

Found: C, 63.7; H, 6.12; N, 18.76%.

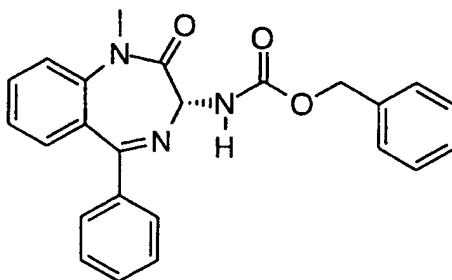
Isomer B:

m.p. 92-95°C, $[\alpha]_D^{25} +81.3^\circ$ (c=0.31, MeOH).

Anal. Calcd. for C₂₇H₃₁N₇O₂•0.35 mol TFA:

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Found: C, 63.31; H, 6.01; N, 18.66.
C, 63.35; H, 6.02; N, 18.74%.

EXAMPLE 107

3R-(+)-3-(Benzyloxycarbonylamino)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepine

To a stirring solution of 3-(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (2.0 g, 7.5 mmol) in methylene chloride (45 mL) at 0°C was added benzyl chloroformate (1.2 mL, 8.3 mmol) and the reaction was allowed to warm to room temperature. The reaction mixture was diluted with methylene chloride (150 mL), and extracted with saturated aqueous sodium hydrogen carbonate (150 mL). The aqueous portion was extracted with methylene chloride (2 x 100 mL) and the organics were combined, dried with magnesium sulfate, gravity filtered, and the solvent was removed in vacuo. The resulting oil was chromatographed over silica with 1:1 ethyl acetate:hexane, yielding a white foam (3.0 g, 99.7%) [α]_D +57.5° (c=1.17; MeOH).

Anal. Calcd. for C₂₄H₂₀N₃O₃ • 0.70 mol H₂O • 0.15 mol CHCl₃:

C, 67.62; H, 5.06; N, 9.8.

Found: C, 67.6; H, 5.02; N, 9.75%.

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The following compounds were prepared substantially as described in Example 81.

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EXAMPLE 108

N-[2,3-Dihydro-1-methyl-2-oxo-5-ethyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide

m.p. 156-158°C.

10 CHN: Anal. Calcd. for $C_{21}H_{21}Cl_2N_3O_2 \cdot 0.5 H_2O$:

C, 59.02; H, 5.19; N, 9.83.

Found: C, 58.99; H, 4.89; N, 9.88.

EXAMPLE 109

15

N-[2,3-Dihydro-1-methyl-2-oxo-5-t-butyl-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide

m.p. 170-171°C.

CHN: Anal. Calcd. for $C_{23}H_{25}Cl_2N_3O_2 \cdot 0.7 H_2O$:

20 C, 60.18; H, 5.80; N, 9.16.

Found: C, 60.17; H, 5.30; N, 9.30.

EXAMPLE 110

25 N-[2,3-Dihydro-1-methyl-2-oxo[4'-(4,4-dimethyl-2-oxazoliny)phenyl]-1H-1,4-benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide

m.p. 188-190°C.

CHN: Anal. Calcd. for $C_{30}H_{28}N_4O_3Cl_2$:

C, 63.95; H, 5.01; N, 9.94.

30 Found: C, 63.96; H, 5.02; N, 10.08.

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EXAMPLE 111

N-[2,3-Dihydro-1-methyl-2-oxo-5-(4-methoxyphenyl)-1H-1,4-
benzodiazepin-3-yl]-3-(2,4-dichlorophenyl)propanamide

5 m.p. 188-189°C.

CHN: Anal. Calcd. for C₂₆H₂₃Cl₂N₃O₃•0.45 H₂O:

C, 62.91; H, 4.67; N, 8.47.

Found: C, 61.89; H, 4.78; N, 8.33.

10

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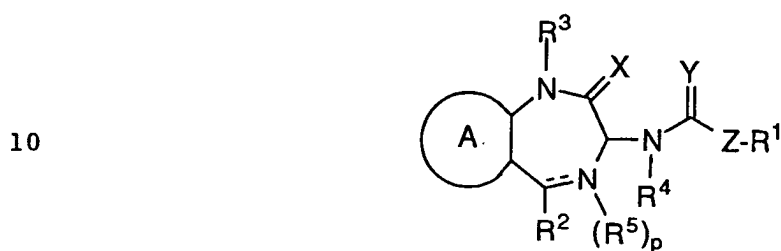
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WHAT IS CLAIMED IS:

1. A method of treating arrhythmia which comprises the administration to a patient in need of such treatment of an effective
 5 amount of a compound of structural formula:



I

- 15 individual diastereomers, enantiomers and mixtures thereof, or a pharmaceutically acceptable salt thereof, wherein

A is

- 20
- 1) thieno,
 - 2) pyrido, or
 - 3) benzo either unsubstituted or substituted with -NH₂, -NHSO₂(C₁-3 alkyl), C₁-3 alkyl or C₁-3 alkoxy;

X is

- 25
- 1) = O,
 - 2) = S,
 - 3) = N-NH₂,
 - 4) = N-OH or
 - 5) = H₂;
- 30

Y is

- 1) = O,
- 2) = N-CN or
- 3) = H₂;

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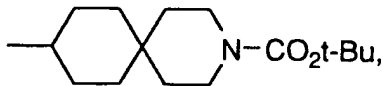
Z is

- 1) C₁-6 alkylene, either straight or branch chain and either unsubstituted or substituted with phenyl or spiropiperidine,
- 5 2) C₂-4 alkenylene, either straight or branch chain,
- 3) $-(CH_2)_m-W-(CH_2)_n-$ wherein m and n are independently 0, 1, 2, 3 or 4 and W is -O-, -S- or -NH,
- 4) 4-(5-methylisoxazole-3-yl),
- 5) C₃-6 cycloalkylene, or
- 10 6) single bond;

p is 0 or 1;

R¹ is

- 15 1) phenyl, either unsubstituted or substituted with one or two substituents selected from
 - a) -NO₂,
 - b) -Cl, Br, F, or I,
 - c) -CF₃,
 - 20 d) -C₁-3 alkyl,
 - e) -C₁-3 alkoxy,
 - f) -CN,
 - g) -methylenedioxy,
- 2) C₅-7 cycloalkyl,
- 25 3)


- 4) mono- or bicyclic heterocyclyl of 5 to 10 members one or two of which are sulfur, nitrogen or oxygen, the remaining being carbon, such as 2-thienyl, 2-furanyl, 2-indolyl, 2-quinoxolinyl, or 2-(2,3-dihydro benzofuranyl)
- 30 5) methyl, or
- 6) indan-5-yl;

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R² is

- 1) phenyl, either unsubstituted or substituted with C₁-3 alkoxy or 4,4-dimethyloxazolin-2-yl,
- 2) C₁-4 alkyl, either straight or branched chain and either
5 unsubstituted or substituted with C₁-3 alkoxy or C₁-3 alkoxy-C₁-3 alkoxy,
- 3) C₅-7 cycloalkyl,
- 4) 2- or 3-furyl,
- 5) 1-methylpiperidin-2-yl, or
- 10 6) if R² is phenyl, the 2-position of the phenyl can be joined to the 4-position nitrogen of the diazepine ring through a carbonyl group and the double bond between the 4-nitrogen and the 5-carbon becomes a single bond;

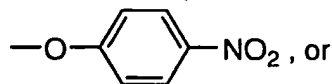
15 R³ is

- 1) hydrogen or
- 2) C₁-3 alkyl either unsubstituted or substituted with -N(CH₃)₂, -OH, -CF₃, or
- 3) -CF₃;

20

R⁴ is

- 1) hydrogen,
- 2) C₁-6 alkyl, the chain of carbon atoms of which can be interrupted by one or two non-adjacent oxygen atoms and
25 which is either unsubstituted or substituted with C₁-3 alkoxy carbonyl, -OH or



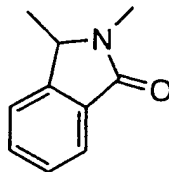
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- 3) tetrazol-5-yl; and

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R⁵ is hydrogen or oxygen or is joined to R² to form the partial structure:

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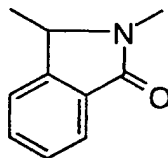


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; and the bond represented by ---- is:

- 1) a double bond when p is zero or when p is 1 and R⁵ is oxygen, or
- 2) a single bond when R⁵ is hydrogen or R⁵ is joined to R² to form the partial structure:

10



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2. The method of treatment of Claim 1 wherein:

20

A is benzo;

X and Y are oxygen;

25

R³ is methyl;

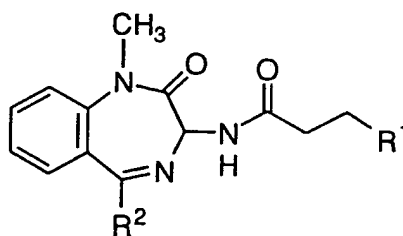
R⁴ is hydrogen; and

R² is C₁-6 alkyl.

30

3. The method of Claim 2 wherein the compound is selected from those depicted in the following Table:

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TABLE

10

R ¹	R ²
2,4-diClPh	-CH ₃
2,4-diClPh	-C ₂ H ₅
2,4-diClPh	-t-Bu
4-CF ₃ Ph	i-C ₃ H ₇
cyclohexyl	i-C ₃ H ₇
2,4-diClPh	i-C ₃ H ₇

15

20

4. The method of treatment of Claim 1 wherein:

A is benzo;

X and Y are oxygen;

25

R³ is methyl;

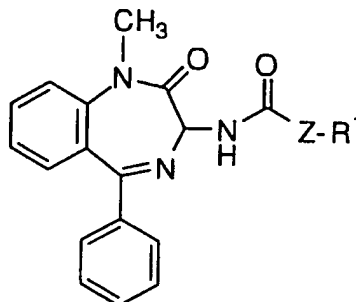
R⁴ is hydrogen; and

30

R² is phenyl.

5. The method of Claim 4 wherein the compound is:

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wherein Z is C₁-6 alkylene or a bond and R¹ is phenyl, phenyl
 10 substituted with -Cl, -Br, -I, -F, or -CF₃, or R¹ is cyclohexyl.

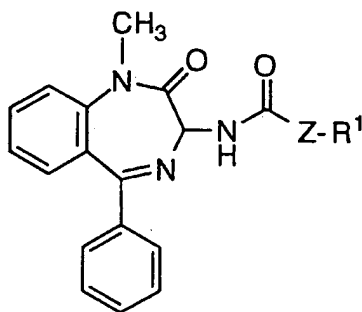
6. The method of Claim 5 wherein the compound is
 selected from those depicted in the following Table:

15	Z	R ¹
	-(CH ₂) ₂ -	2,4-diClPh
	-(CH ₂) ₂ -	4-ClPh
	-(CH ₂) ₂ -	2,4-diFPh
	-(CH ₂) ₂ -	2-ClPh
20	-(CH ₂) ₂ -	4-CF ₃ Ph
	-CH ₂ -	4-CF ₃ Ph
	-(CH ₂) ₂ -	3-CF ₃ Ph
	-(CH ₂) ₂ -	2-CF ₃ Ph
	-(CH ₂) ₂ -	cyclohexyl
25	-	cyclohexyl
	-(CH ₂) ₃ -	cyclohexyl
	-CH ₂ -	cyclohexyl
	-(CH ₂) ₂ -	Ph
	-CH ₂ -	Ph
30	-(CH ₂) ₂ -	4-NCPh
	-(CH ₂) ₂ -	3-ClPh
	-(CH ₂) ₃ -	Ph
	-(CH ₂) ₂ -	3-NCPh
	-(CH ₂) ₂ -	2-thienyl

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7. The method of Claim 4 wherein the compound has structural formula:

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wherein Z is C₂₋₄ alkenylene and R¹ is phenyl or phenyl substituted with -Cl, -Br, -F, -I, -CF₃, C₁₋₃ alkyl, C₁₋₃ alkoxy, nitro or methylenedioxy.

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8. The method of Claim 7, wherein the compound is selected from those depicted in the following Table:

	<u>Z</u>	<u>R¹</u>
5	-CH=CH-	4-NO ₂ Ph
	-CH=CH-	2,4-diClPh
10	-CH=CH-	3-ClPh
	-CH=CH-	2-ClPh
15	-CH=CH-	2,4-diFPh
	-CH=CH-	2,6-diClPh
20	-CH=CH-	4-CF ₃ Ph
	-CH=CH-	2-BrPh

25

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	<u>Z</u>	<u>R¹</u>
	-CH=CH-	4-IPh
5	-CH=CH-	4-BrPh
10	$\begin{array}{c} \text{-C=CH-} \\ \\ \text{CH}_3 \end{array}$	Ph
	-CH=CH-	Ph
15	-CH=CH-	3,4-diClPh
	-CH=CH-	4-CH ₃ Ph
20	-CH=CH-	4-CH ₃ OPh
	-CH=CH-	3,4-methylenedioxyPh
25	-CH=CH-	3-BrPh

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9. The method of Claim 1 wherein:

Z is -NH-.

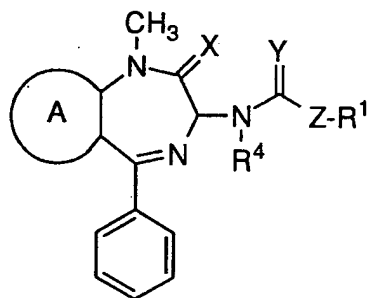
10. The method of Claim 9 wherein the compound is selected from those depicted in the following Table.

10						
15	A	R ¹	R ²	R ³	R ⁴	Y
	benzo	3-CH ₃ Ph	Ph		H	O
	benzo	2,4-diClPh	Ph	-CH ₃	H	O
20	benzo	3-CH ₃ Ph		n-C ₃ H ₇	H	O
	benzo	-CH ₂ Cyclohexyl	Ph	-CH ₃	H	=N-CN
25	benzo	3-CH ₃ Ph	Ph	-CH ₃	H	O
	benzo	5-indanyl	Ph		H	O
30		3-CH ₃ Ph	Ph	-CH ₃	H	O

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11. A compound selected from the group consisting of the compounds depicted in the following Table:

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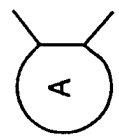
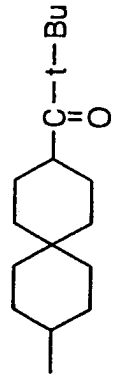
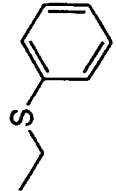

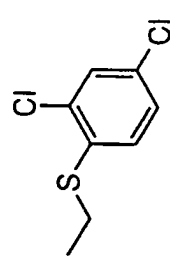
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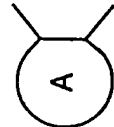
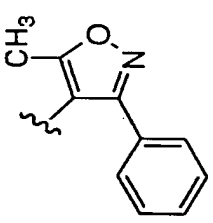

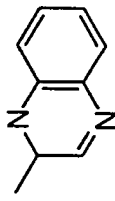
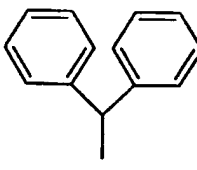
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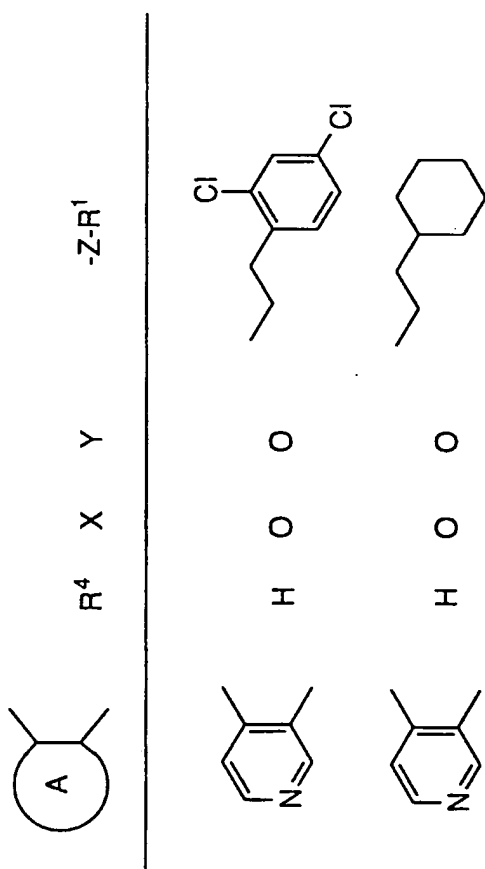
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	R ⁴	X	Y	-Z-R ¹
benzo	H	O	O	
benzo	H	O	O	
benzo	H	O	O	
benzo	H	O	O	

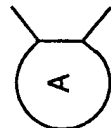
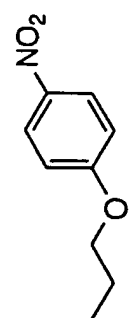
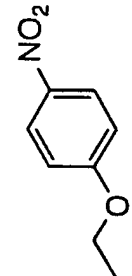
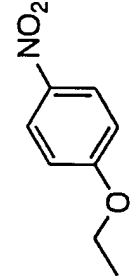
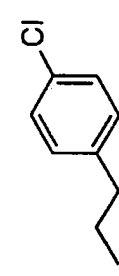
- 167 -

	R ⁴	X	Y	-Z-R ¹
benzo	H	O	O	
benzo	H	O	O	
benzo	H	O	O	
benzo	H	O	O	

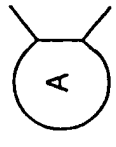
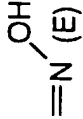
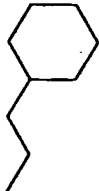
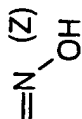
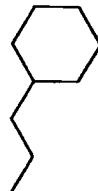
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	R ⁴	X	Y	-Z-R ¹
benzo		O	H ₂	
benzo	H	O	H ₂	
benzo	H	O	H ₂	

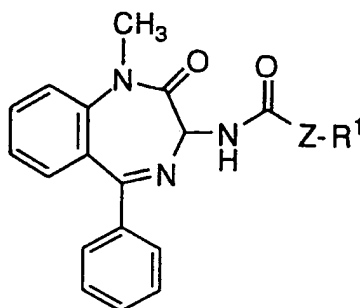
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	R ⁴	X	Y	-Z-R ¹
benzo	H		O	
benzo	H		O	

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12. A pharmaceutical formulation comprising a pharmaceutically acceptable carrier and an effective amount of the compound of Claim 11.

13. A compound of structural formula:



wherein Z is C₁-6 alkylene or a bond and R¹ is phenyl, phenyl substituted with -Cl, -Br, -I, -F, -CN or -CF₃, or R¹ is cyclohexyl.

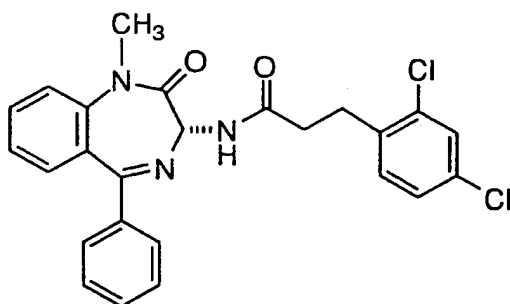
14. The compound of Claim 13 wherein the compound is selected from those depicted in the following Table:

Z	R ¹
-(CH ₂) ₂ -	2,4-diClPh
-(CH ₂) ₂ -	4-ClPh
-(CH ₂) ₂ -	2,4-diFPh
-(CH ₂) ₂ -	2-ClPh
-(CH ₂) ₂ -	4-CF ₃ Ph
-CH ₂ -	4-CF ₃ Ph
-(CH ₂) ₂ -	3-CF ₃ Ph
-(CH ₂) ₂ -	2-CF ₃ Ph
-(CH ₂) ₂ -	cyclohexyl
-	cyclohexyl
-(CH ₂) ₃ -	cyclohexyl
-CH ₂ -	cyclohexyl

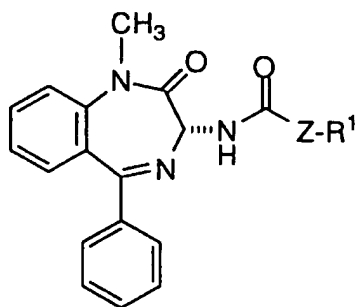
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-(CH ₂) ₂ -	Ph
-CH ₂ -	Ph
-(CH ₂) ₂ -	4-NCPH
-(CH ₂) ₂ -	3-ClPh
-(CH ₂) ₃ -	Ph
-(CH ₂) ₂ -	3-CNPh
-(CH ₂) ₂ -	2-thienyl

15. The compound of Claim 14 of structural formula:



16. A compound of structural formula:



wherein Z is C₂₋₄ alkenylene and R¹ is phenyl or phenyl substituted with -Cl, -Br, -F, -I, -CF₃, C₁₋₃ alkyl, C₁₋₃ alkoxy, nitro or methylenedioxy.

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17. The compound of Claim 16, selected from those depicted in the following Table:

	<u>L</u>	<u>Z</u>	<u>R¹</u>
5	735,801	-CH=CH-	4-NO ₂ Ph
	735,821	-CH=CH-	2,4-diChPh
10	735,865	-CH=CH-	3-ClPh
	735,868	-CH=CH-	2-ClPh
	735,875	-CH=CH-	2,4-diFPh
15	735,894	-CH=CH-	2,6-diClPh
	735,896	-CH=CH-	4-CF ₃ Ph
20	738,048	-CH=CH-	2-BrPh

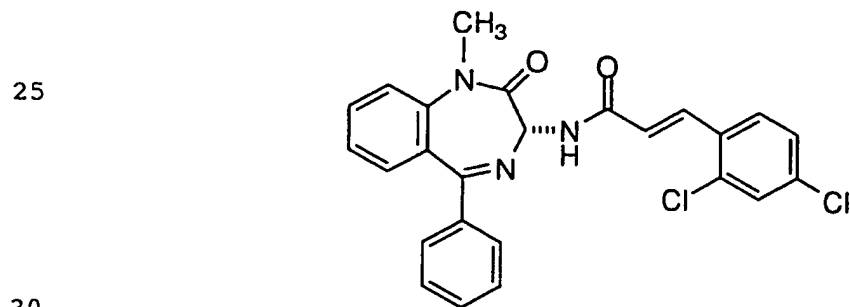
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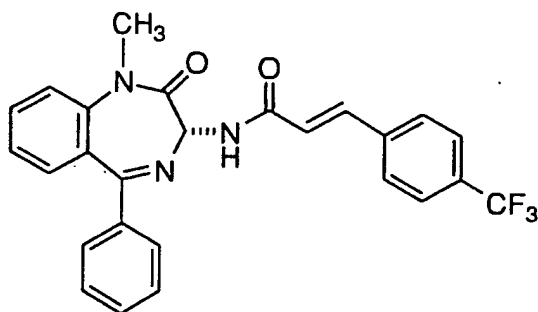
	<u>L</u>	<u>Z</u>	<u>R¹</u>
	738,052	-CH=CH-	4-IPh
5	738,067	-CH=CH-	4-BrPh
	366,333	$\begin{array}{c} \text{-C=CH-} \\ \\ \text{CH}_3 \end{array}$	Ph
10	735,800	-CH=CH-	3,4-diClPh
	735,822	-CH=CH-	4-CH ₃ Ph
15	735,826	-CH=CH-	4-CH ₃ OPh
	742,192	-CH=CH-	3,4-methylenedioxyPh
20	738,049	-CH=CH-	3-BrPh

18. The compound of Claim 17 of structural formula:

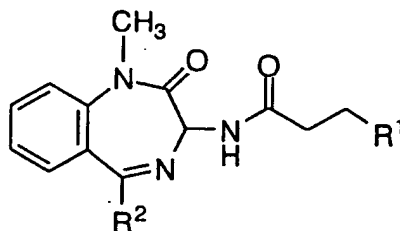


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19. The compound of Claim 17 of structural formula:



20. A compound of structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is

- 1) phenyl, either unsubstituted or substituted with one or two substituents selected from
 - a) -NO₂,
 - b) -Cl, -Br -F or -I,
 - c) -CF₃,
 - d) -C₁₋₃ alkyl,
 - e) -C₁₋₃ alkoxy,
 - f) -CN and
 - g) -methylenedioxy, or
- 2) C₅₋₇ cycloalkyl; and

R² is C₁₋₆ alkyl.

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21. The compound of Claim 20 which is selected from the group consisting of those depicted in the following Table:

	R ¹	R ²
5	2,4-diClPh	-CH ₃
	2,4-diClPh	-C ₂ H ₅
	2,4-diClPh	-t-Bu
	4-CF ₃ Ph	i-C ₃ H ₇
	cyclohexyl	i-C ₃ H ₇
10	2,4-diClPh	i-C ₃ H ₇

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13414

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/55; C07D 243/24
US CL :514/221; 540/509

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/221; 540/509

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN-CAS-ON-LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,220,018 (BOCK et al.) 15 June 1993.	1-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

	Special categories of cited documents:		
*A	document defining the general state of the art which is not considered to be of particular relevance	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*E	earlier document published on or after the international filing date	*X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*L	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*O	document referring to an oral disclosure, use, exhibition or other means		
*P	document published prior to the international filing date but later than the priority date claimed	*Z	document member of the same patent family

Date of the actual completion of the international search

22 DECEMBER 1994

Date of mailing of the international search report

24 FEB 1995

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